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ABSTRACT

These hearings before the Select Committee on Nutrition and Human Needs of the United States Senate include testimony on the subject of research into the use of phosphates to prevent dental decay. The purpose of the hearing was to explore certain dental health questions raised during the committee's recent hearings on the Television Advertising of Food to Children. It was brought to the committee's attention during those hearings that considerable research has been conducted on the possibilities of adding phosphates to various foodstuffs--presweetened cereals and refreshment drinks--to help reduce the problem of dental decay in children. Some of the most extensive research in this area was privately conducted by the General Foods Corporation during the last decade, with the special approval of the Food and Drug Administration. The committee's hearing focuses on these studies. Representatives of the Food and Drug Administration, as well as the General Foods Corporation, testified. These witnesses included: Dr. Lloyd B. Tepper, associate commissioner for science, accompanied by Dr. Ogden C. Johnson, director, Division of Nutrition, Office of Sciences; Dr. Clarence C. Gilkes, dental officer, Division of Surgical-Dental Drug Products; Mr. Gerald F. Meyer, director, office of Legislative Services, Food and Drug Administration, and A. S. Clausi, vice president and director of corporate research, General Foods Corporation. [Two pages of copyrighted materials have been deleted from this document. Some pages may not be clearly legible due to the size of the print.] (Author/JM)

ED 084316

NUTRITION EDUCATION—1973

HEARINGS

BEFORE THE

SELECT COMMITTEE ON NUTRITION AND HUMAN NEEDS

OF THE

UNITED STATES SENATE

NINETY-THIRD CONGRESS

FIRST SESSION

PART 6—PHOSPHATE RESEARCH AND DENTAL DECAY

WASHINGTON, D.C., APRIL 16, 1973

Series 73/NE6

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NUTRITION EDUCATION:

Part 1 and 1A—Overview—Consultants' Recommendations, Dec. 5, 1972; with Appendix.
Part 2 and 2A—Overview—The Federal Programs, Dec. 6, 1972; with Appendix.
Part 3—TV Advertising of Food to Children, March 5, 1973.
Part 4—TV Advertising of Food to Children, March 6, 1973.
Part 5—TV Advertising of Food to Children, March 12, 1973.
Part 6—Phosphate Research and Dental Decay, April 16, 1973.

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SELECT COMMITTEE ON
NUTRITION AND HUMAN NEEDS
April 11, 1973.

HEARING ON PHOSPHATE RESEARCH AND DENTAL DECAY SCHEDULED

Senator George S. McGovern (D.–S.D.), chairman of the Select Committee on Nutrition and Human Needs, announced today, a committee hearing on Monday, April 16, to take testimony on the subject of research into the use of phosphates to prevent dental decay.

Senator Richard Schweiker (R.–Pa.) will chair the hearing scheduled to open at 9:30 a.m. in room 1318 of the Dirksen Building.

The purpose of the hearing will be to explore certain dental health questions raised during the committee's recent hearings on the Television Advertising of Food to Children.[1]

It was brought to the committee's attention during those hearings that considerable research has been conducted on the possibilities of adding phosphates to various foodstuffs—presweetened cereals and refreshment drinks—to help reduce the problem of dental decay in children.

Some of the most extensive research in this area was privately conducted during the last decade by the General Foods Corporation with the special approval of the Food and Drug Administration. The committee's hearing will focus on these studies.

Representatives of the Food and Drug Administration, as well as the General Foods Corporation will testify.

[1] See page II for schedule of hearings.

NUTRITION AND DISEASE

Phosphate Research and Dental Decay

MONDAY, APRIL 16, 1973

U.S. SENATE
SELECT COMMITTEE ON
NUTRITION AND HUMAN NEEDS
Washington, D.C.

The Select Committee met at 10:15 a.m., pursuant to call, in room 1318 of the Dirksen Building, the Honorable Richard S. Schweiker presiding.

Present: Senators Schweiker and Percy.

Staff members: Kenneth Schlossberg, staff director; Marshall Matz, assistant counsel; Vernon M. Goetcheus, chief, minority staff; and Elizabeth P. Hottell, professional staff.

Senator SCHWEIKER. The Select Committee on Nutrition and Human Needs will please come to order.

I want to begin by apologizing for the delay in the hearings. Normally, I am very punctual, however this morning the administration elected to announce 274 base closings around the country. Each State and Appropriations Committee member was well briefed on which States were affected—32 States were, including my own—thus I had to be there to hear some of the bad news. I do apologize for being late, but, under the circumstances, there wasn't much I could do about it.

OPENING STATEMENT BY SENATOR SCHWEIKER, PRESIDING

I would like to open by thanking Senator McGovern for asking me to chair today's hearing of the Senate Select Committee on Nutrition and Human Needs.

Today we will hear testimony on research into the use of phosphates to control dental decay. Last month this committee held hearings on television advertising of food to children which raised questions about dental health. Specifically, we raised questions about the effect of presweetened foods on children's teeth. At that time, the subject of adding phosphates—a potential tooth strengthener—to various foodstuffs as a means of deterring tooth decay was brought up. We are going to look further at phosphate additives today.

The General Foods Corporation has conducted extensive research on phosphate additives with the approval of the Food and Drug Administration, and representatives of both FDA and General Foods are here today.

General Foods has conducted tests in the area of phosphate additives with both cereals and beverages, and we will be examining those

tests. One specific test, which was part of a series of eight tests on cereals, relates directly to the committee's hearings last month. This particular test showed that children eating presweetened cereals tended to have more cavities than those eating nonpresweetened cereal, even though each child had sweetened the nonpresweetened cereal according to his own taste. These results are of great concern to me, and to the other members of this committee.

In addition, General Foods conducted tests adding phosphates to certain beverage products. Results from these tests showed that when phosphates are added to fumaric acid—a frequent beverage additive used to produce tartness—the phosphate lessened the damaging effect of the acid on tooth enamel. Fumaric acid is a less expensive substitute for citric acid which is found in numerous beverages sold to the public daily.

Although the hearings today are directed toward phosphate research, I do not feel that additional facts concerning food products which are raised by this research should go unnoticed, especially in light of this committee's previous hearings on dental decay in children.

I feel that General Foods Corporation should be commended for their research in this field, and for their willingness to discuss their findings with the committee. Their tests and findings can be most useful to all companies and individuals concerned with making our food products as nutritious and beneficial as possible.

Senator Percy?

STATEMENT OF SENATOR PERCY

Senator PERCY. Senator Schweiker, I am very pleased to be here this morning. I know of your own particular great interest and expertise in this field, and I know you have made a major contribution.

I would like to join you in welcoming General Foods this morning. I have had a working relationship with management of General Foods for over 20 years. Claire Frances, board chairman, and I served in starting educational television in this country—when we spent $22 million of the Ford Foundation money in starting with this new concept.

If I have any conflict of interest at all, it should be revealed that their past chairman has been a director of Bell and Howell Company, and has been a very, very close friend of mine for many, many years.

But I look on the research that has been done in this field as exceedingly important. We are grateful that General Foods will share it with the general public and with us. Also, if I have any critical questions, my friendship with the company will not in the least deter me from asking them. We are here to learn as much as we possibly can.

Thank you.

Senator SCHWEIKER. Thank you, Senator Percy. I'd like to call, then, as our first witness, Dr. Lloyd B. Tepper, associate commissioner for science, Food and Drug Administration, Public Health Service. Dr. Tepper, we welcome you to the committee. Again, I apologize for the delay, we normally are not tardy.

I wish you would identify your associates for the record.

STATEMENT OF DR. LLOYD B. TEPPER, ASSOCIATE COMMISSIONER FOR SCIENCE, ACCOMPANIED BY DR. OGDEN C. JOHNSON, DIRECTOR, DIVISION OF NUTRITION, OFFICE OF SCIENCES; DR. CLARENCE C. GILKES, DENTAL OFFICER, DIVISION OF SURGICAL-DENTAL DRUG PRODUCTS; AND MR. GERALD F. MEYER, DIRECTOR, OFFICE OF LEGISLATIVE SERVICES, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Dr. TEPPER. Mr. Chairman, thank you. I'd like to introduce Dr. Ogden C. Johnson, to my right, who is director of the Division of Nutrition with the Bureau of Foods. To my left, Dr. Clarence C. Gilkes, dental officer, Division of Surgical-Dental Drug Products, Office of Scientific Evaluation, Bureau of Drugs; and Gerald F. Meyer, director of the Office of Legislative Services.

We shall attempt to answer whatever questions you might have.

We are very pleased to appear before you this morning to discuss a new drug application (NDA) and investigational new drug (IND) applications submitted to the Food and Drug Administration (FDA) by General Foods Corporation. These petitions concern the addition of monosodium dihydrogen phosphate to certain pre-sweetened breakfast cereals and beverage mixes for the purpose of inhibiting dental caries. We will aslo attempt to address the committee's broader interest regarding the use of refined sucrose in foods. The Department of Health, Education, and Welfare (DHEW) certainly shares the concern of this committee with problems of health and nutrition which affect our population, including dental health and tooth decay.

Specifically, I should like to draw attention to the efforts conducted by the National Institute of Dental Research and the National Caries Program, which are specifically concerned to a large degree with the problem of dental caries.

APPLICATION ON PHOSPHATES SUBMITTED BY GENERAL FOODS

Now, first this morning, with respect to the petitions on phosphates which were submitted by General Foods. In regard to the possible value of phosphates in reducing dental caries, General Foods Corporation first submitted an IND application to us on September 21, 1964, to study sodium phosphates in a variety of prepared breakfast cereals for the purpose of inhibiting dental caries.

On September 20, 1965, 1 year later, the firm submitted an NDA proposing the use of monosodium dihydrogen phosphate in five presweetened breakfast cereals, namely, Post Alpha Bits, Post Crispy Critters, Post Sugar Crisp, Post Sugar Sparkled Flakes, and Post Sugar Sparkled Rice Krinkles.

FDA's review concluded that the clinical data submitted were insufficient to support the effectiveness of the substance, and the claims made in labeling. The application was considered "incomplete" and a letter was issued on May 19, 1967, notifying the sponsor of this fact.

This application was amended on January 3, 20, and 27, 1969, and finally resubmitted on February 12, 1969, with the specific claim that the substance—that is, the phosphate—" . . . reduces cavities in children and adults who eat presweetened cereals."

The FDA review concluded that the application was "not approvable" because of deficiencies in clinical data and labeling. There were problems in this research which focused on a rather high dropout rate among participants in the study. In any study, one must be cautious when there is a loss of people who entered the study at the beginning.

There was some question as to objectivity in the judgment of the progress, in the character and extent of the caries in the mouth; the readings of the conditions of teeth seemed to be variable, and interpretation criteria were insufficient.

The caries rate, even in controls, seemed to be progressing at a rate which, if carried on for a number of years, would have removed all the teeth from the mouths of these children. The curve, when plotted from year to year, in other words, was such that a much higher caries rate was experienced than might be noted in any selected population. This implied that the readings of the condition of the teeth was not well controlled. There was some question as to the judgments which were made upon examination of the teeth of the participants in the program.

At any rate, General Foods withdrew their New Drug Application in a letter dated August 14, 1969.

The corporation also submitted three IND applications in late 1966 to study the use of monosodium dihydrogen phosphate in a noncarbonated, flavored, instant soft drink mix (Kool-Aid), its artificially-sweetened counterpart (Pre-sweetened Kool-Aid), and an orange-flavored breakfast drink mix (Tang). The purpose for adding this substance to these drinks was to inhibit dental caries.

In June 1970, the sponsor notified FDA that these studies were discontinued because of the presence of cyclamates in the product. The letter further stated that one of the investigators for these studies found that the beverage products used in certain of the studies without the additives resulted in a higher incidence of caries than the same products with the additives. Although the sponsor did not complete its review of these studies, it elected to add the substance to the products without making any specific nutritional claims for effectiveness of the additive.

Monosodium dihydrogen phosphate is Generally Recognized As Safe (GRAS) for use in food products and, provided no therapeutic claims are made, may be added without further FDA approval.

Your staff has asked why, based on the sponsor's letter, FDA did not alert the industry and/or the public to the fact that General Foods learned that certain presweetened cereals and beverages resulted in a slightly higher incidence of tooth decay. In the simplest of terms, we do not believe this study was conclusive and it contains some contradicting evidence.

I mentioned there was some doubt as to the rate of caries development. There was some question as to whether or not the observers knew the preparations which the subjects were receiving. In other words, if an individual interpreting the condition of the teeth actually knew the group with which the subject was associated, there might be some introduced bias.

Also, there was not entirely controlled consumption evidence. That is to say that, in studies of this type, one may infer that subjects eating presweetenened cereal may have a higher caries rate. This may be true, but it may be due to the fact that these children are eating more

cereal. Perhaps these cereals are more appealing to those who eat them, and therefore the quantity consumed of the presweetened variety is greater than that which is consumed as sweetened by the consumer himself.

This may occur even though preweighed boxes are distributed to the participants. It is also unclear as to what extent other variables, such as the diets of participants in the study, may have affected the results obtained.

At any rate, the FDA did not accept data submitted in the NDA as sufficient basis to approve the substance as a drug; and, conversely, could hardly consider the additional information learned as a basis for a major public or industry warning. Additionally, we believe there is a fairly widespread understanding that products containing increased amounts of refined carbohydrates are more likely to contribute to increased acidity in the mouth and subsequent tooth decay—discounting all other factors such as proper dental hygiene. Furthermore, we are concerned about the total phosphate intake in the diet and its relationship to the metabolism of other minerals.

In this context, additional phosphate may be very good for the teeth, but we are also concerned about the relationship of phosphates to the total body welfare, not just the teeth.

Refined Carbohydrates in Foods

Now a few remarks about sugar in foods in general. With regard to the broader issue of the use of refined carbohydrates—that is, sugar—in foods, the committee should understand that this is a complex matter. First of all, sucrose, the principal simple sugar, is naturally present in many foods; and, whether occurring naturally or added, would have the same affect. There is nothing peculiar or distinctive about sucrose added as opposed to sugar which is an intrinsic constituent of a food material.

An evaluation of the effects of various foods on the prevalence and severity of dental caries must also take into consideration not only the composition of the total diet, but such factors as the frequency and length of exposure to the food, the dental hygiene practiced by the individual, and the fluoride content of the available water supply.

In considering the relationship of sugar to the total diet, it is apparent that an increase in the proportion of processed food in a diet will almost certainly lead to an increase in sugar consumption. The role of sugar as a functional ingredient in baked products, such as cakes and cookies, is essential and usually cannot be reduced without adversely affecting the product. The use of sugar as a sweetening agent to increase the acceptability of certain foods has been practiced for a long time both by manufacturers and consumers. This includes the use of table sugar on products such as breakfast cereals, fresh fruit, or home prepared desserts.

Sugar as a component of confectionery products provides sweetness, and, in some cases, texture. In all cases, the sugar that is present is a possible contributor to the problem of dental caries. In this regard, the dental profession has been actively working to educate the public to use more effective procedures of dental hygiene and limit their intake of food components which contribute to increased dental caries.

Modification of the diet is obviously an individual's responsibility. Ingredient labeling of food products does provide the consumer with useful information if there is a concern for the presence of sugar in a product. For most foods in the marketplace, the presence of sugar is identified in the product ingredient statement. For other foods, such as some of the standardized, canned fruit products for which such labeling is not required, the presence of sugar is understood by the consumer since the product is packed in what is defined as a "sirup."

Many of these products, in addition, do carry an indication that sugar is a component of the "sirup." For some products, it is virtually self-evident by nature of the product that sugar is a major component. This is particularly true of candy and confectionery products and of many dessert products which are considered by the consumer to be high in calories because of their sweetness and high sugar content.

Concern has also been expressed at the apparent increasing quantity of sugar consumed through the wider use of fabricated foods. Some have suggested that restraints should be put on the amount of sugar that is present in food in order to change the consumption pattern. However, such restraints on the use of refined sugar must be carefully considered in relation to the total diet. Those individuals who are now consuming a diet adequate in calories and are at an acceptable body weight would have to replace the eliminated sugar calories with other food calories. Those which are available are in protein, fat, and carbohydrate in more complex forms such as starch.

The replacement of sugar calories by protein would lead to a marked increase in the cost of the diet as protein is a more expensive dietary component. In addition, some health professionals question the desirability of raising protein levels to above the current level—which is more than adequate for much of the population.

It would seem unreasonable to consider increases in the consumption of fat as a substitute for needed calories. Concern about an excessive fat intake in the American diet has been raised by a number of experts in the field of diet and heart disease.

Thus, the replacement of sugar with more complex carbohydrates would seem to be the only alternative in replacing needed calories, if the intake of simple sugars such as sucrose were reduced.

Unfortunately, starch cannot replace sugar as a functional ingredient nor as a sweetener in most of the products which consumers find desirable, and now purchase for routine use in their regular diet. Furthermore, such a total diet change would have to involve a major change in food consumption patterns with greater utilization of cereal products, such as bread and pasta; and a reduction in consumption of other products, such as canned fruits in sirup and baked products with a high sugar content. There would also have to be a marked reduction in the consumption of carbonated beverages, sweetened fruit drinks, and confectionery products—all of which make sizable contributions to the refined sugar in the total diet.

Difficulties to Implement Change

To bring about this kind of change is not simple, and is not likely to result from just calling attention to the presence of sugar. It would seem reasonable to assume that those who strongly advocate such dietary changes should be prepared to carefully consider and define

what changes would be necessary, and to recommend educational and informational programs for consumers to see whether such changes can be made acceptable in relation to the normal diet patterns within the United States.

This committee is aware of the materials which are used by our population which have demonstrable adverse health effects. Certainly tobacco is high on the list. The connection between the consumption of tobacco products and clearly deleterious health effects is quite apparent. Cigarettes are so labeled, yet it is apparent that such labels and the limited propaganda efforts, which we have launched in this direction, do not have a great influence on tobacco consumption patterns in this country.

The committee should also understand that, except for fluoride, no substance has been conclusively shown to have a definite protective effect against tooth decay in man. Nevertheless, available evidence does justify the additional research now underway on several substances including organic and inorganic phosphates.

Of course, the phosphate approach is only part of the total problem of tooth decay. If the committee so desires, we could go into additional detail into the nature of the decay process which obviously concerns the tooth itself—the microflora, the biological flora within the mouth, and the total spectrum of foods which are consumed. Certain constituents of these foods support the nutrition of man. They also support the nutrition of the oral microflora which contribute to tooth decay.

Unfortunately, the testing of dietary constituents is very difficult, since few human subjects are willing to eat one particular food regularly for the length of time required for a properly designed controlled study.

If additional substances are discovered with anticaries properties, there will remain the problem of how the factor can be applied. Unless the substances can be put in essentially all cariogenic foods, their effect would very likely be much reduced.

We are, of course, interested in the investigation of any substance which might promote improved dental health and we will do our utmost to expedite the evaluation of any agent which might be safely and effectively used for this purpose.

We do not believe that an attempt to label products with a quantitative statement of the exact amount of carbohydrates present in the products is a reasonable approach, since not only the amount of carbohydrates but the quantity of food consumed and the tendency of the food to adhere to the surface of the tooth are all factors which vary—and may be just as important in contributing to dental caries.

The important point here is that the absolute or relative amount of sucrose in any preparation is not necessarily the most relevant factor. We are concerned here with the timing, the duration, during which time such materials are in the mouth. One could eat a whole box of cookies at one sitting, and probably be much better off than eating a half a cookie every half hour.

Significance of Food Adhesiveness

Another important attribute of food materials is the adhesiveness of the food material itself. A statement of sucrose content does not have relevance to the adhesive properties of the food material which

would reflect the propensity of the ingested material to adhere to the surface of the tooth. Of course, adherence of the substance to the tooth is highly relevant to the ability of the oral micro-organisms to synthesize organic acids which demineralize the tooth surfaces.

We do believe that presenting information on all food labels that clearly identifies sugar as a major component is a significant step towards the goals supported by those concerned about refined sugar and dental decay. This, together with appropriate education and information programs on dental hygiene and care, diet, and efforts to provide the benefits of fluoridation to increased segments of the population, should provide a realistic and comprehensive approach to the reduction of dental caries.

Mr. Chairman, we will be pleased to try to respond to any questions which you or your group might have.

Senator SCHWEIKER. Thank you very much. Senator Percy, would you like to ask questions at this point?

Senator PERCY. Mr. Chairman, when you have the Chair you ought to seize the opportunity.

I would like to ask what the average person can do to most easily and best protect himself against the possibility of decay from sugar.

I attended a luncheon one time, as I mentioned in one of our hearings, with the president of the American Dental Association, who said that most of the damage that is done after a meal is done in the first hour or so. He said that if a person would simply reach out and, take a glass of water after a meal, and swish water around their mouth they would accomplish 95 percent of what could have been accomplished by brushing their teeth, actually. And it's so much easier.

And I noticed that out of 1,500 people at the banquet, 1,495 within the next 3 or 4 minutes, grabbed a glass of water and swished it around, after the sweet dessert.

Is something as simple as that helpful and effective?

INITIATION OF DECAY PROCESS

Dr. TEPPER. Yes, your information is absolutely correct, Senator Percy. We are concerned here with the capabilities of micro-organisms within the mouth to synthesize organic acids which demineralize the tooth surface. This initiates the caries process.

Anything which can be done to undo the capacity of these micro-organisms is obviously beneficial. If we remove the substrate—the growth material, sucrose—upon which these micro-organisms thrive, we are way ahead of the game.

Now, one does this by rinsing his mouth after eating. One does this by restricting the frequency during the day at which times persons eat such material. In other words, have a legitimate dessert at the conclusion of lunch, or dinner, and then omit nibbling during the course of the day and bedtime snacks.

One can also reorient the kinds of foods he wishes to eat, to choose a selection of foods which have less substrate for the microflora. This involves major changes in our public eating habits. Do we want, in the middle of the afternoon, a bowl of oatmeal rather than a candy bar? It might be very good for the teeth. I'm not sure we could sell this to the public broadly considered, at the present time.

But the point of attack is limiting the amount of sucrose available to the micro-organisms of the mouth. You do this by brushing, limiting the frequency of exposure, and choosing foods which have less adhesive properties, less sticky foods which might adhere to the tooth surface.

Senator PERCY. Well, the children, early in life, are conditioned. We always say: "Brush your teeth three times a day." Obviously, if you brush them at the end of the meal, it's better than some other time, like before a meal. But suppose we were conditioned to simply use water as a wash—which is readily accessible after every meal—after the consumption of every sweetened product. Ever since I heard the president of the American Dental Association, I have so conditioned myself. I never eat anything without drinking water after that and swishing around a little bit. And I have a feeling that I have performed a service that is very simple and easy.

Wouldn't it be possible to condition children—who are addicted to television—with public service telecasts of this kind? This could solve many of these problems.

Dr. TEPPER. It would probably be a very good idea. The question is: Under what auspices is an effective campaign conducted? Also: How effective is such a campaign.

Now, I drew an analogy to tobacco products. And certainly we have launched a campaign to do something about this. It has not been notoriously successful. Certainly when we look at the improper use of alcholic beverages, we also have campaigns. Yet they do not seem to have much impact on reducing the number of alcohol-related auto fatalities.

So the question is really a very fundamental one. It is: What is the role of the Government in education along these lines? And: What is the most effective medium whereby patterns of behavior can be actually changed?

Senator PERCY. I would hope that General Foods and other companies that have such a close working relationship with the National Advertising Council could take the problem to them. Possibly they could tell us whether research would show that a simple step like this might not be helpful; also come up with a way to communicate that idea.

EXTEND WATER FLUORIDATION PROGRAMS

Dr. TEPPER. We would hope that rinsing would be more effective. Unfortunately, rinsing is part of the battle, but it's not the secret to control of caries in this country. I might mention here that if we are really concerned about caries prevention, the extension of the water fluoridation program to areas in which it does not now esixt would be immensely helpful—much more so than swishing water around in the mouth.

Senator PERCY. Would you give me an opinion on beverages. Is it your opinion—after reviewing all of the available scientific evidence—that certain beverages tend to cause tooth decay in humans?

Dr. TEPPER. Again, the critical issue here, Senator, is that of sucrose in the mouth. It seems that the organisms with which we are concerned exist preferentially on sucrose. Now the question, then, is: Through what media does sucrose enter the mouth?

And, as a reply to your question, surely any beverage containing sucrose contributes to dental caries. This includes fabricated beverages. This includes natural fruit juices which contain sucrose. The acids in such fruit-derived beverages, in addition, contribute to the demineralization of the tooth surface.

Senator PERCY. But what is the principal ingredient in beverages, the culprit that causes decay?

Dr. TEPPER. Really two, I would say. One is the acidic content of natural and fabricated beverages. Second, the sucrose which, again, is the preferential substrate for the streptococci in the mouth, which are the fundamental generators of tooth decay acid.

Senator PERCY. Without affecting adversely the marketability of the products, is it possible to make a substitute for these substances which are injurious?

IN PLACE OF SUCROSE—ARTIFICIAL SWEETENERS

Dr. TEPPER. In part, yes, and in part, no. Certainly one can use artificial sweeteners to cover some of the requirement for sweetness. It's also true that the careful adjustment of acid in fruit drinks can to some degree reduce the requirements for using sweeteners in the fruit beverage.

Perhaps on this one I might ask Dr. Ogden Johnson if he would have some additional remarks; speaking as a nutritionist familiar with the technology involved in the preparation of beverages.

Senator PERCY. Would you comment on the addition of phosphate to beverages, as a way to eliminate or reduce the tendency to cause tooth decay?

Dr. TEPPER. The evidence at the moment is not conclusive.

The work which was described did have serious built-in problems. Individuals who were evaluating the populations were not completely unaware of whether subjects were in test or control populations. It's very easy for bias to be introduced when the persons interpreting the phenomena are familiar with the group with which the subject is associated.

Also, there was no good quantitative control in these particular studies. Thus the evidence, at this point, is not conclusive that phosphates—in and of themselves—have a particular influence on caries.

We then have to seriously face the issue of whether phosphates should be added to natural juices. Should we phosphate orange juice? Is this a desirable procedure?

And there is the issue of total phosphate in the diet. How much phosphate do we really believe is desirable in the diet? Oral considerations aside.

In this connection, the balance of calcium and phosphate in the diet is rather critical, and the promotion of phosphate addition, so that the balance between phosphate and calcium is disturbed, may not be totally desirable.

Senator PERCY. I am assuming that there is a tendency for greater tooth decay in presweetened cereals. I am assuming that with nonpresweetened cereals the sugar is added by many of the consumers, because it isn't presweetened.

Is there a greater tendency for tooth decay in the presweetened? If so, then why would it be—assuming that sugar is probably added to the nonpresweetened cereal?

Dr. TEPPER. Well, we are not sure that that is, in fact, the case. In other words, the studies are inconclusive.

Furthermore, there may be more tooth decay among people eating presweetened cereals because they happen to like them, and they may eat twice as much as the controlled population which happens to sweeten their own corn flakes.

At the present time, we have no evidence as to whether or not this is the explanation, and we are not even sure that a dissimilarity exists.

Senator PERCY. You mean they might just like it more?

Dr. TEPPER. They just may like it more.

Senator PERCY. Is there an indication they may eat it instead of candy?

CONTINUOUS APPLICATION TO TEETH

Dr. TEPPER. That is correct, and this gets back to the chronicity of exposure.[1] In other words, Junior is put in front of a television set with a box of this kind of preparation. It is not so much that it is presweetened. The fact is that it is continually being applied to the surfaces of his teeth so that the oral micro-organisms continue to thrive.

Senator PERCY. Then I suppose you get into the question: What would the individual be eating if they weren't eating cereal? Also, are they getting more nutrition out of the cereal than they would out of a straight candy bar?

Dr. TEPPER. Which is the alternative?

Senator PERCY. Well, I suppose those questions are beyond our level of scientific research now. We thank you very much for being here, and I thank our chairman for his indulgence in letting me question first.

Senator SCHWEIKER. Thank you, Senator Percy.

Doctor, there are several things relating to the study that I would like to ask you about. Dr. Gilkes in his evaluation study for FDA states, and I quote:

> The results indicated that the subjects eating presweetened cereals tend to have more cavities than subjects using nonpresweetened cereals. The caries rate for the presweetened cereal controls is very high. Hence the question comes to mind, is it possible the use of phosphates in the sweetened cereals merely cancels the damaging effects of the presweetened cereals.

I wonder if you would like to comment on his evaluation study for FDA.

Dr. TEPPER. Insofar as I am able to judge, these studies were entirely inconclusive for the reason which was suggested to Senator Percy. In other words, the quantitative aspects were unknown even though the materials might have been prepared in uniform boxes. The readings of the phenomena in the oral cavity were not clearly standardized, and there was very strong possibility of bias in these studies.

Senator SCHWEIKER. Well, further in the evaluation of the research Dr. Gilkes says:

> With the exception of study number two the controls were individuals using presweetened cereals, These cereals themselves may be detrimental. Hence the test is usually not for a caries control measure, but for an agent which may reduce the harmful effect of presweetened cereals. The cariogenic effect of the sweetener is shown clearly in the results of study number two, and the major concern of the

[1] See Part 3.—TV Advertising of Food to Children, pp. 276-305

FDA will be the nature of the claim. If the company claims that the agent reduces caries when added to the cereals should they not also reveal that the presweetened cereals without the agent probably increases caries.

Would you comment on that?

Dr. TEPPER. I'm not sure I thoroughly understood the question.

Senator SCHWEIKER. The last part of the statement is the key part. I realize I am reading rapidly. If the company claims that the phosphate agent reduces caries, when added to the cereals, should they not also reveal that the presweetened cereals without the agent probably increases cavities?

Dr. TEPPER. Yes, I think when studies are conducted one must reveal the good along with the bad. One is obligated to report the totality of results. The question here is the quality of all results, positive or negative.

Senator SCHWEIKER. You say the studies are inconclusive. Are they statistically inadequate? Are they medically inadequate? Is the scientific sampling inadequate? On what basis are the tests inadequate?

CONTROL SITUATION NECESSARY FOR TESTS

Dr. TEPPER. I will make some remarks, and then I think we will call upon Dr. Gilkes. To begin with, when one attempts to compare the presence or absence of a phenomenon those individuals who make the readings as to whether this phenomenon exists or does not exist must be completely isolated from knowledge as to whether or not he is looking at a given time at the test population or control population. If he knows that he is looking at a test population which is being given something which is supposed to reduce caries there may be a propensity on the part of the reader to underread caries and say "my gosh, that's fine preparation." When these studies are conducted they must be totally blind studies where the reader does not know what is being given to the subjects.

Now we have serious doubts that the blind nature of this study was maintained throughout. We have some doubts as to the criteria on which readings were made. I said earlier that, if one plots the caries rate year by year, apparently this rate existing in any population is completely inconsistent with what is observed in the control group. That is to say there were no clearly standardized methods for reading what went on in these subjects regardless of which group they happened to be in.

Also, we were very much concerned about the dropout rate. If you commit yourself to a scientific study with 400 people and at the end of a period of time 200 people are gone, they have just dropped out of the study, you are very much concerned with the design of the study, the motivation of the study, you are concerned about which ones dropped out, which ones remained. Were there reasons for certain dropouts? You cannot conduct a valid study when your subjects disappear at this rate.

In sum, Dr. Gilkes and his colleagues were very much concerned about the statistical basis, the experimental design, the controls, the criteria for making any kind of judgment about oral phenomena at all.

With your permission, may we ask Dr. Gilkes to perhaps expand as to elements of the study which he found unsatisfactory.

Senator SCHWEIKER. Do I understand that the FDA is concurring in the study? Or that the study does conclusively show, by FDA's analysis, that eating presweetened cereals does tend to cause more caries than the subjects using nonpresweetened cereals? Are you in agreement with that phase of the study?

Dr. TEPPER. No, sir; we are not.

Senator SCHWEIKER. You are not?

Dr. TEPPER. As I indicated, one of the reasons that we are not is that we have no secure knowledge as to the quantity of consumption in the respective diets.

Senator SCHWEIKER. Well, I have read from Dr. Gilkes' evaluation of the test. Now, does someone else in FDA disagree with his evaluation?

Dr. TEPPER. Perhaps we could straighten out this point, if we ask Dr. Gilkes.

Senator SCHWEIKER. All right, I agree with that.

Dr. GILKES. The study started out with 626 participants for 24 months. It ended up with 315. There were 311 dropouts. Hence, half of those were on nonpresweetened cereals and half were on the presweetened cereals. So what I am getting at is that only half of 315 actually were on the presweetened cereals. Do you follow me?

MORE STUDIES INDICATED

So with the dropout rate plus the fact that there was no dietary analysis and poor supervision of the study, we were not in a position to indict the firm based on this single study. By that I mean this was the only study that used a nonpresweetened breakfast cereal versus the presweetened cereals, and in a study on dental caries, you should have more than one study to demonstrate efficacy, as is required by the regulations. So if we require at least two studies to demonstrate efficacy of the product then I don't think we would want to indict a firm or an investigator because his study showed about .5 of a surface of a tooth difference between the control group and the presweetened cereal.

Senator SCHWEIKER. How much?

Dr. GILKES. Point five of a surface. Now when we are talking about surfaces of teeth we are speaking of five surfaces of the teeth being involved, the biting surface, the front of the tooth, the back of the tooth, the tongue side, and the cheek side. Now with five surfaces involved there the difference between claiming of efficacy, say, for some of the toothpastes that have been approved by FDA was about .78 of a surface, was improved by the product. Hence if there was a difference of less than half, about .5, then considering this was an isolated study we didn't feel that this was conclusive evidence when we had all of these variables that weren't considered such as the dietary analysis, lack of supervision—that is to say to be certain, as Dr. Tepper indicated, that they didn't consume more of the presweetened cereal than those who were consuming the nonpresweetened cereal.

So the study just didn't loom in our estimation as one to go out and ask for a hearing against the firm because of the many problems that we found inherent in the study.

Dr. TEPPER. The study notwithstanding, sir, I don't think you have to be a great scientist to appreciate the fact that a highly sweetened

sucrose containing material which is naturally tacky when it gets wet is going to be a troublemaker. And I would not prescribe this particular food component for my own children, not on the basis of scientific studies, but because I do not believe that prolonged exposure of tooth surfaces to a sucrose containing material of this sort is beneficial.

Dr. GILKES. As a result of our findings when they resubmitted their application for second consideration they changed the labeling claims to state "reduces the incidence of dental caries for children and adults who eat presweetened cereals." This was entirely different from the original claim because the original claim was that it reduces the incidence of dental caries, period. But when we raised questions of this presweetened cereal causing a problem they, too, must have had some evidence that gave them the same indication, hence they changed their labeling claim.

Senator SCHWEIKER. In view of what has been done so far, did the study indicate that it would be a worthy field to pursue further?

Dr. TEPPER. There are interesting experimental bases for suggesting this might be a reasonable partial approach to control of dental caries—and I emphasize partial. A very small piece of the action. If one were to devise prospective tests we would hope that they would be well designed, well controlled. We have in fact offered assistance, some of the members of our organization have offered assistance in the past with respect to statistical development of a design which would produce studies which were in fact valid. These are very complicated studies, and they take a long period of time, and it is not always easy to get access to the proper population.

To answer your question, yes, there is reason on the basis of work which has been done previously to encourage a petition by industry to continue with work along these lines. We would simply hope that work which was contemplated would be well designed and well executed; underlining here the fact that again we are also concerned about phosphate in total diet, not just for——

Senator SCHWEIKER. Would you explain that further? You mentioned that in your earlier testimony. What is your concern; and, specifically, what are you talking about?

CONCERN OVER MINERAL BALANCE

Dr. TEPPER. Well, when one starts manipulating a particular constituent in the diet it is always prudent to inquire as to whether you are affecting other constituents of the diet as well. When we are concerned about total mineral metabolism, we are interested in the balance between various mineral constituents which are ingested. If we look at animal data for a moment and examine the ratio between calcium and phosphorus intake, we believe this is very important to the overall nutrition of the test animal. The optimal calcium nutrition is obtained when there is approximately a 1 to 1 ratio between calcium and phosphorus. When the ratio is 1 to 2—in other words, one calcium to two phosphorus, there is some loss in development of the animal. And when there is one calcium to three phosphorus this will not readily support life in these test animals. Therefore, we are concerned with the overall proposition of phosphorus containing compounds in the diet, not just in the teeth. We are concerned here about the sequestration of calcium.

There is also some evidence that iron metabolism is affected by phosphate in the diet. Since we do exist in sort of a borderline iron nutritional state as it is, we are not particularly eager to do anything which will cause the additional sequestration of iron from the diet.

So I am talking here about a total overall approach to our nutritional pattern rather than emphasis on one aspect.

Perhaps Dr. Johnson would have something to add to that.

Dr. JOHNSON. I think in this regard it is important to remember that if one is going to add an ingredient such as phosphorus to many products, if it is in one product, it may not be much of a problem, but if one wanted to add this to all products that contained sucrose, it could lead to a substantial increase in the phosphorus intake and this would lead toward the problem that Dr. Tepper was referring to.

Senator SCHWEIKER. Isn't it true that a lot of today's processed products have a high rate of phosphorus? I am not quarreling with your 1 and 1 ratio for metabolic balance. I concur with that. But, by that same yardstick, are we as strict with a lot of other products on the market which contain phosphate? My information indicates that phosphorus is coming out of our ears—in terms of processed products. Why put a double standard here on presweetened cereals and not apply the yardstick to other cereals and phosphate, and a lot of other things?

Dr. TEPPER. There are a couple of things. First of all, you will notice that this material which appeared to be a breakfast food was coming through the Bureau of Drugs. Now why was this? This was because a specific therapeutic claim was being made for these cereals, the kind of therapeutic claim which called for a demonstration of safety and efficacy. This is the law which applies to a drug, and the fact is that when a specific therapeutic claim is made, we are dealing under the drug law.

Now, with respect to foods where no specific therapeutic claim is made, one can use the identical added substance if it is in fact generally regarded as safe, and these phosphates are generally regarded as safe.

I would only amend that remark by saying that nutritionists are very much interested in the total phosphate intake, and I assure you that this issue is not escaping attention.

Senator SCHWEIKER. I would like to yield to the committee staff director for several questions on the Tang-Kool-Aid study.

SOFT DRINK STUDY SHOWED HIGH CARIES INCREASE

Mr. SCHLOSSBERG. Dr. Tepper, on the Tang-Kool-Aid study I believe you referred to a slight increase in the incidence of cavities in both these studies. My understanding of the Tang and Kool-Aid study was that—according to an article that is about to be published by the researcher who did that study—the increased incidence of caries by Tang and Kool-Aid was in the order of 43 or 92 percent. That is more than a slight increase, is it not? What I am driving at is: While the study on the presweetened cereals—I think we would all agree—showed a tendency which is by no means conclusive; nonetheless, the study on the drink products was conclusive. Was it not related in terms of the increased caries?

Dr. TEPPER. May I ask Dr. Gilkes to respond to that?

Mr. SCHLOSSBERG. If you wish.

Dr. GILKES. The beverage drink mixes never got to the new drug application stage. They were always in the investigational new drug application stage. They implied a labeling claim that it would reduce the incidence of caries; and, since it was an IND, they were not required to submit the raw data. Now, when they submitted some explanation of their data there was no summary as to the reduction of caries. Some of the studies that are going to be published now by these gentlemen who were involved in these studies are with regard to the acids involved on animals, and we can't extrapolate that data to man. And at no time did they submit the raw data to the Food and Drug Administration with summaries making claims.

Dr. TEPPER. There is nothing fundamentally different about these products when compared with lemonade.

Mr. SCHLOSSBERG. But there is a difference: Is fumaric acid in lemonade?

Dr. TEPPER. Citric acid and fumaric acid in lemonade?

Mr. SCHLOSSBERG. What I am pointing out is that there is a difference, in terms of the effect that citric acid and fumaric acid have on animals.

Dr. GILKES. Demonstrated on animals only, and as I indicated to you, there is no perfect animal model to extrapolate the data to man for caries. Hence what they saw in rats' teeth comparing fumaric acid, citric acid, and several others, we can't draw an analogy to humans and say we are going to expect to see the same thing because we don't have a perfect animal model.

Dr. TEPPER. This caries problem develops whenever the acidity in the mouth as measured by *pH* drops below about 5.7. And it doesn't matter what acid you use to produce this change; when it occurs there would be some demineralization on the surface of the tooth. And we can talk about any of these commercially prepared preparations, we can talk about lemonade, we can talk about orange juice, and I would be very hard put to have to distinguish one from the other as far as its capability for producing these kinds of dental changes.

Mr. SCHLOSSBERG. Apparently the researchers who did this study for General Foods did not have that difficulty—insofar as the animal test. Now let me quote from the study that is about to be published. They say, "all of the acids resulted in enamel dissolution, *but fumaric acid was more deleterious than citric at equivalent concentrations.*"

Dr. GILKES. Is that relating to animal studies?

Mr. SCHLOSSBERG. Yes, it is.

It is, also, my further understanding that the clinic tests—which there will also be a published study—show essentially the same results.

PRODUCT CHANGES MADE DUE TO ANIMAL STUDIES?

However, is it not true: There was sufficient concern, both in the company and among the researchers who conducted the study for Tang and Kool-Aid, that the products were reconstituted—following the results of the study on animals?

Dr. GILKES. I would think perhaps the company could best answer that. It didn't cause us any alarm because we didn't get the raw data, and only when we have patient record forms which would indicate who received the test product and who received the control—that is to say the test product would be without the active ingredient—and then when we can count the cavities compared to the control group, can we come to a conclusion. We do not accept the sponsor's summary nor his statistical analysis. He can offer it, and that is why we are given 180 days to review a document, and we go over it and arrive at our conclusions. But in an investigational new drug application we do not have to go over this type data. They have to submit a progress report which would give us a summary of their data, and in no case do we find the magnitude of incidence of caries that you cited there.

Dr. TEPPER. Now the other point worth raising, I think, is if a material enters commerce as a food these materials are all generally regarded as safe constituents of a food and we have no particular jurisdiction to judge one as being any different from the other.

Mr. SCHLOSSBERG. Can you answer this: Tang is marketed as a replacement for orange juice, as a superior breakfast drink—nutritionally, it may be having more vitamin C than orange juice. If the study also showed that Tang tended to cause more cavities than plain orange juice, doesn't the parent also have a right to know the other side of this product?

Dr. TEPPER. I suspect the individual does have a right to know this. The parent also ought to know that a candy bar causes more caries than a bowl of oatmeal.

Mr. SCHLOSSBERG. Or an apple.

Dr. TEPPER. Or an apple.

So these are all areas in which consumer education is the means by which we attempt to influence consumption patterns by the public.

Dr. GILKES. This data was never submitted to us, and hence we couldn't arrive at either approval or disapproval because they never went to the NDA stage, and when they withdrew the therapeutic claim it no longer came under the jurisdiction of the Bureau of Drugs. Once they took off the claim that it "reduced the incidence of dental caries" it wasn't in our jurisdiction any longer.

Mr. MEYER. If I may, let me add to this point. Obviously, if the food is unsafe we can take action. I think the question here is whether or not the evidence that you are speaking of, the animal data, would be a basis for action. I don't think it would be. As Dr. Gilkes has said, evidence in other studies indicates that for purposes of tooth decay one can't readily extrapolate from the animal to man. To obtain clinical evidence the studies involved would have to be sufficiently well controlled that one could conclusively say that Tang was responsible for higher incidence of tooth decay. If that comes out, I am sure the FDA would be seriously concerned about whether such a warning label should be required.

WHEN IS RESPONSIBILITY TO PUBLIC'S INTEREST SHOWN?

Mr. SCHLOSSBERG. Tang and Kool-Aid products were changed by General Foods on the basis there might be a problem. I think our concern is not that General Foods didn't act responsively; but, that

if there is a problem with this particular mix of constitutents—especially one type of acid, fumaric acid—then the public should be alerted. I know Tang and Kool-Aid were changed; however there is High C and Welch Ade, which are comparable to the uses of Tang, and both of these products still contain fumaric acid. This study was completed 3 or 4 years ago. Tang and Kool-Aid have been changed, but these two products have not. Where is the public's interest shown here? At what point, when you have research that shows deleterious effect, is there responsibility to alert the public?

Mr. MEYER. Was the fumaric acid data from animal tests?

Mr. SCHLOSSBERG. They were animal tests.

There were clinical tests as well. Clinical tests were conducted; and the results are going to be published. My understanding from the researcher, the dentist in Elkhart, is that the clinical test will essentially show the same result as the animal test. Also Dr. Mueller, who is the noted researcher in this area, told me personally and directly that if he had seen the results from the animal test he would never have proceeded with the clinical tests because the results would have been so clear.

Dr. TEPPER. Yes, but it is precisely this kind of investigation which we will want to scrutinize specifically to be sure that the work which is conducted represents a clean, well designed study. We have been trapped on this before.

Mr. MEYER. I think the point we have to make is that if we are to take any regulatory action, including requiring cautionary labeling, we would have to be certain that the data presented was sufficient to sustain our position in court. Up to this point we don't have that kind of evidence.

Senator SCHWEIKER. Senator Percy has one last question.

Senator PERCY. Doctor, just one last question. We don't want to inhibit our other witnesses.

Could you define for the committee, in the simplest possible terms, precisely what FDA does require in order to decide that a substance has—as you put it in your own statement—a definite protective effect against tooth decay in a human?

Dr. TEPPER. This means that it is being marketed as a drug, and this means that safety and efficacy must be demonstrated. With respect to efficacy there must be at least two well-designed studies on humans which demonstrate this.

Now as Dr. Gilkes mentioned, we concern ourselves in the raw data. We are not concerned with summaries or testimonials by pundits on the subject. We must have the raw data for our own evaluation.

Senator PERCY. Thank you very much indeed.

Senator SCHWEIKER. Thank you, gentlemen, very much. We appreciate it.

The General Foods Company, will they please come forward and identify their witnesses?

STATEMENT OF A. S. CLAUSI, VICE PRESIDENT AND DIRECTOR OF CORPORATE RESEARCH, GENERAL FOODS CORPORATION

Mr. CLAUSI. Mr. Chairman, members of the committee, my name is A. S. Clausi. I am vice president of General Foods Corporation and director of Corporate Research. In my 27 years with General Foods I

have held various technical positions, including 12 years within the Post cereals division. I am author of seven U.S. patents on General Foods products, including such as Post Oat Flakes and Post Alpha-Bits presweetened cereals.

My office is at the corporation's Technical Center at Tarrytown, N.Y., where we have more than 650 scientists and other technical personnel who are engaged largely in scientific work in the area of the basic science on food products and nutrients, new product development, nutritional improvement of our products, and quality assurance.

Let me say I welcome this opportunity to speak to this group about the research that General Foods has done on the use of phosphates as possible nutritional additives in cereals and in beverages to help improve the dental health of the population.

I think it is rather important that we go through a rather detailed chronology of what actually happened in the research, gentlemen, since much of what has been presented to you could very easily lead to some confusion on several points that we think are very key to understanding this whole matter.

My statement consists of three parts.

First, a description of the research done, which, as I say, I think is very important for us to spend some time on that.

Second, the conclusions that we drew from that research.

Third, the actions that General Foods has taken as a result, and what we intend to do in the future. I will try to skip those parts that I don't think are particularly germane to the story, and if the recorder-secretary will bear with me I will jump around a bit.

Senator PERCY. Mr. Chairman, I think if it would be acceptable the entire statement, of course, would be put in the record. Would you prefer to have it inserted in the record as given, and then just summarize and pick out some of the highlights for us?

Mr. CLAUSI. I would like to read in detail certain parts.

Senator PERCY. That's fine.

Senator SCHWEIKER. That is perfectly all right. Would you prefer to have the entire statement in the record?

Mr. CLAUSI. I prefer to have the entire statement in the record.[1]

Senator SCHWEIKER. I am going to ask Senator Percy to take the Chair for a while.

Senator PERCY. All right fine. I think I will have to leave about 11:59. So that perhaps—would you like to take maybe 10 minutes to hit some of the highlights, and then I have only about 10 minutes of questions.

Mr. CLAUSI. I will try, sir.

Senator PERCY. All right, fine, sir. Thank you very much.

INTEREST IN FOODS CONTAINING PHOSPHATE

Mr. CLAUSI. The history of interest in phosphate is detailed in my statement. I think it is important, though, that we should say that the work that General Foods funded in part—and I would like to stress that point, that we funded in part—was carried out by reputable dental researchers at the Indiana University School of Dentistry, people who were involved in such discoveries as stannus fluoride, a widely used tooth strenghtener today, and other research

[1] See prepared statement, p. 570.

in the area. It was for this reason, and also our interest in exploring phosphates in foods, that we decided in 1961 to proceed with the Indiana University researchers. The tests were designed by the Indiana University researchers. The funding and the samples prepared for these tests came from General Foods, the samples in totality, the funding in part.

We started with ready-to-eat breakfast cereals. One might ask well, why did we start with ready-to-eat breakfast cereals? It was our belief that if phosphates were to be proven successful they should be available in a commonly consumed food and one that would be consumed by the prime target groups, namely, children 6 to 15, whom we felt had the greatest need for nutrient strengthening in the dental health area.

We started with animal tests, which although we realized they were not directly translatable to the human environment, we felt that the step was well to add in order to be sure that we were on the track of an agent that at least looked encouraging. When these results indicated that phosphates could be helpful, Indiana University proposed human clinical tests.

The first pilot test was started in Bloomington, Ind., in 1962. One group was given cereals enriched with phosphates at various levels, since we were still reaching for the optimal level. We used presweetened cereals in this case, and as is usually the case, we had a second control group that received the same cereals without the phosphate additives. This was an ad lib type of study, since, as was pointed out in earlier testimony, it is almost impossible to get people to eat the same food day after day, so that we felt that a variety was needed. We also felt that an in-home real life situation was required in order to be able to make claims that would be meaningful to consumers if proven successful.

Based on early findings that seemed to show positive results a second clinical test was started in South Bend, Ind., in 1963. Now here we used what we felt was the optimum level of phosphates. We also had multiple panels. That is, we had panels that had presweetened cereals and the additive, and without the additive. We had panels that had non-presweetened cereals with the additive and without the additive, and we had the full line with the additive and not the additive. And it is in this study, and this study only, that any comparisons are even possible between presweetened cereals and non-presweetened cereals.

Shortly thereafter, in 1964, we started four more clinical studies. We started one study in Fort Wayne, Ind., which was a fluoridated water area. This was with presweetened cereals both with and without the agent. Our objective here was to determine the efficacy within a fluoridated water area.

In Goshen, Ind., we separated the agent from the cereals in order to establish whether it operated systematically via capsules or whether there was a need to have it multiple times during the day, and also to see if there was any interaction between the vehicle ready to eat cereals and the agent.

In Muscatatuck, Ind., at an institution we had the most highly controlled test. This was where through supervision we made sure that the people in the study received at least one serving of the cereals a day. This was not an ad lib situation, in other words.

Finally, in 1964 we started a study in North Dakota under totally different researchers. This was not under Indiana University's supervision, and this was done to assure ourselves of as much objectivity in the results as could be obtained.

Now 5 months later, in September of 1964, we filed an IND, claimed investigational new drug application. This was required by the then new Federal regulations which had just come into effect, and these covered all of the clinical research being conducted at that time.

Request FDA Permission To Market

Our reports continue to be favorable from our studies. What is more, the phosphate we used in the cereals appeared to be particularly effective in reducing or inhibiting caries on the surfaces between the teeth, the surfaces that cannot normally be reached with normal brushing. Both Indiana University and General Foods believed with conviction that we had developed a method of contributing to the dental health of the population, and we felt justified in asking the FDA for permission to market cereals containing monosodium phosphate nutrient, which was the agent Indiana University had identified as being the most efficacious in presweetened cereals.

FDA was given a briefing on the whole research program in November of 1964. At that time we were told that there would have to be a minimum of 2 years clinical tests. So the work continued. When the time was up we worked very carefully with Indiana University and prepared our new drug application, which is that which is required before a product can be marketed making therapeutic claims.

While this was going on our laboratory work was also continuing, and we found in work with a wide range of beverages, acid sweetened beverages, both natural and synthetic, that the phosphate agent appeared to be effective in mitigating against some of the erosion tendencies that we saw in these products.

So in October 1966 we filed an IND to cover work that we planned to start on the soft drink mixes, and clinical test commenced in 1966 in Elkhart, Ind. And here again we tested the soft drink mixes with and without the phosphate, along with the control panel that received no drink mixes at all. We ran some additional tests to further evaluate the effectiveness of the agent outside of the food product.

In the meantime FDA had not yet acted favorably on our original new drug application which was for presweetened cereals with the monosodium phosphate. I have to stress that. This was for presweetened cereals which were the only tests that we had sufficient time and results on, we felt, in order to meet FDA's criteria. In May 1967 the FDA rejected our NDA as being incomplete. Both General Foods and Indiana University believed that the FDA's action was based on the form of our NDA, that is, on the manner in which we presented the data rather than the content.

So we diligently went about changing our application. Suddenly a rock slide blocked the path. In the summer of 1969 one of the primary clinical investigators of Indiana University raised questions about the interpretations of the clinical test results. The questions were aimed at the manner by which the X-rays and the clinical examinations had been interpreted by the Indiana University dentists doing the re-

search. Abruptly, the validity of the data, especially the favorable conclusions, was now under question.

With this cloud hanging over the entire program of research, General Foods felt obligated to withdraw its New Drug Application from the FDA until we could clear up the entire situation. Therefore, with the concurrence of Indiana University, General Foods in August 1969 informed the FDA that it was voluntarily withdrawing its NDA for presweetened cereals.

Now we set about reanalyzing the data. We brought in outside investigators from Canada, from Australia. We reached for maximum objectivity from people who were known in the field but who had no previous contact with the data or with any of the researchers. Work was randomized by trained statisticians, so that the new observers had no idea of what samples of X-rays represented what subjects in the test.

As a result of their reanalysis, Indiana University concluded that certain portions of their clinical program could have been affected by an unconscious bias. It was felt that this could have been caused by the fact that the individuals examining the X-rays and the clinical examinations may have had access to the codes that had been used to disguise the subjects in the various panels. Thus a bias could have affected the results.

Now for our conclusions. As I stated earlier, in our original New Drug Application for presweetened cereals with the FDA, which also covered all of the other tests that were in progress via IND, we reported that the laboratory animal and human clinical tests had produced favorable results. Specifically, we felt that monosodium phosphate when consumed in both regular and presweetened cereals was effective in reducing human dental caries. It was particularly effective on the surfaces between the teeth where normal brushing did not reach.

Second, our tests indicated that the phosphate was absorbed by the body's system, it was a systemic effect and recirculated to the tooth structure. This we felt we had confirmed in the Goshen test using the capsule. And I might add at this point that although none of the tests were designed to expressly identify this point we found no differences statistically between consumption of presweetened and non-presweetened cereals in the only panel that such a comparison could be drawn. We also found no difference in caries incidence between low, medium or high consumption cereal users.

Actually these findings have been published in the Journal of the American Dental Association in 1967 and in 1968.

Data Reanalysis Shows Little or No Effect

However, when we reanalyzed this suspect data with objective researchers we found that the cereals enriched with the monosodium phosphate produced virtually no effect on inhibiting human caries, and this applied to both presweetened and nonsweetened breakfast cereals.

Now for beverages, the original conclusions indicated a beneficial effect in reducing caries. But the reanalysis did not fully support these original conclusions. The reanalysis showed some statistical trends that phosphate additives seemed to mitigate the demineralization

effect on the teeth which was believed to be caused by the acid in the beverages. As you know, many beverages contain acids of various kinds; citric acid in fruit juices, lactic acid in milk, phosphoric acid in some carbonated soft drinks, and other acids in other natural fruit juices. There is evidence that the acid in natural fruit juices and other beverages dissolves some of the minerals in the enamel of the teeth, and we found that the use of phosphate indicated some mitigation of this demineralization action.

Now I would like to spend the last few minutes talking to you about the actions that have been taken by General Foods.

All of the testing by Indiana University had used the nutrient monosodium phosphate as the active ingredient. As I just said, it appeared to have some effect on the demineralization caused by the acid in the beverages, even after the reanalysis of the suspect data. Therefore, General Foods decided to add monosodium phosphate to those powdered soft drink beverages it had been testing. That is after we had overcome some taste problems caused by the use of this nutrient in the beverages. We started adding monosodium phosphate to our powdered beverages in 1969, and then some more in 1970, and completed the job in 1971.

Let me say here that despite 10 frustrating years down a largely unproductive path, General Foods did not stop research aimed at improving the nutritional content of our products and their effects on dental health. We have continued our laboratory work on animals, the only indicator we have for screening devices, seeking the effectiveness of other nutrients in beverages.

We have discovered, we feel, another phosphate which appears to be more effective than monosodium phosphate in counteracting the effect of acid on teeth enamel. This is monocalcium phosphate. In our animal studies, laboratory rats consuming a soft drink enriched with monocalcium phosphate showed less demineralization and often less cavities than rats consuming natural fruit juices.

Both calcium and phosphorous, as you know, are required mineral nutrients needed by man. The human body contains both calcium and phosphorous. Most of the body's calcium is found in the bones, although the mineral has roles in many other functions of the body.

The human requirement for calcium varies from about 400 mg per day for an infant up to as much as 1,400 mg per day for teenage boys. And I believe the new standard that is being proposed under the nutrient regulations will be about 1,000 mg per day.

Numerous dietary and health surveys have indicated that many individual diets are lacking in calcium. For instance, the 1965 U.S. Department of Agriculture dietary survey suggested that calcium and iron were the nutrients most often found below dietary requirements, and this is usually attributed to insufficient ingestion of milk and milk derived products.

In other words, we felt that outside research pointed toward possible favorable results that we had experienced in our animals and that these were consistent with the dietary needs.

So that in 1972, the tail end of last year, we began enriching our powdered beverages with this new agent, monocalcium phosphate. These are the products that are now on the market.

I want to emphasize here and now that we are not making any claims that monocalcium phosphate will inhibit human caries. We just don't know. But it is a well known nutrient, as I have indicated earlier, both from the calcium and the phosphorous viewpoint and from the balance of both, and it is needed in the diet, in our opinion.

In the meantime, General Foods continues laboratory explorations of many different nutrient compounds, seeking to further improve our products. Thank you very much.

PREPARED STATEMENT OF A. S. CLAUSI

Mr. Chairman, members of the committee, and staff, my name is A. S. Clausi. I am vice president of General Foods Corporation and director of corporate research. In my 27-year career with General Foods I have held various technical research positions, including 12 years as director of research for the Post cereals division. I am the author of seven U.S. patents on General Foods products, including Fortified Oat Flakes and Alpa-Bits presweetened cereals.

My office is in the corporation's Technical Center at Tarrytown, N.Y., where we have more than 650 scientists and technically trained personnel. They are engaged largely in scientific work in the areas of basic research on food and nutrients, new product development, nutritional improvement of our products, and quality assurance.

I welcome this opportunity to tell you about the research work on the use of phosphates as nutritional additives in cereals and beverages to help improve the dental health of the population. Some of this research has been done by General Foods Corporation scientists. And some of it was financed in part by General Foods and conducted by Indiana University's Dental School.

My statement consists of three parts.

First, a description of the research done.

Second, the conclusions we drew from that research.

Third, the actions taken by General Foods as a result and what we intend to do in the future.

Mr. Chairman, General Foods has had a long time policy of underwriting and conducting research on food products and their components. It has always been General Foods' practice to develop new products and improve existing ones so as to provide consumers with wholesome, nutritional food products. In fact, the founder of the predecessor company of General Foods, Mr. C. W. Post, established our policy 78 years ago when he insisted on the development of nourishing, wholesome foods that met human needs.

DESCRIPTION OF RESEARCH

It was in line with this policy that General Foods Corporate Research Department in August 1959 proposed a laboratory research project to determine whether phosphates as nutritional additives could provide a benefit to the dental health of the Nation. At this time, there were scientific reports about the use of phosphates in bread in Sweden to reduce dental caries. But even before then, as early as 1955, medical and scientific journals had reported elsewhere on the use of phosphates as potentially effective agents to inhibit dental cavities. Therefore, to determine the validity of these various reports, in September 1960 General Foods Corporate Research started its first laboratory animal study on phosphates. Hardly had we started when a new opportunity presented itself.

Just one month later, October 1960, the Post Division of General Foods received a letter from Dr. Joseph C. Muhler, D.D.S., professor of the department of biochemistry at the Indiana University Medical Center. He proposed a joint research project on phosphates in cereals. Dr. Muhler felt that cereals would provide the best type of food product to test the effectiveness of phosphates to inhibit dental cavities. He reasoned that ready-to-eat cereals were widely consumed, particularly by children and by lower income groups. Both groups needed better preventive dental care.

In November 1960 I met with Dr. Muhler to discuss his suggestions. Then in January 1961 Dr. Muhler submitted to General Foods his first written proposal on the phosphate research with cereals.

General Foods, after detailed consideration, decided that a joint project with Dr. Muhler and Indiana University promised the best avenue for the company to follow toward the goal of helping improve the dental health of the population. While we were experts in food products and their components, we had little expertise in dental health. On the other hand, Dr. Muhler and the University of Indiana had a worldwide reputation for their research in the field of preventive dental medicine. They had developed the use of stannous fluoride to reduce dental caries, an achievement which had been recognized by the American Dental Association and other health organizations.

Therefore, in September 1961 General Foods signed an agreement with Indiana University Foundation to cooperate on phosphate dental health research. Dr. Muhler felt he had identified several phosphate compounds that would prove beneficial for dental health. The test products were to be manufactured by General Foods. The tests would be designed and conducted by Indiana University with partial funding by General Foods. If the phosphates were proven to be effective in preventing or reducing cavities, Indiana University Foundation would grant licenses to General Foods in return for royalty payments, according to this agreement.

General Foods then supplied Indiana University with ready-to-eat breakfast cereal products containing phosphates to test on laboratory animals. The initial tests were in vitro, that is, on teeth removed from the animals. When the initial results looked promising, further tests were then conducted in vivo, that is, on the animals themselves.

It may be asked: Why were these tests made in this order? Well, General Foods wanted to have a high degree of confidence that the phosphates were successful in preventing dental decay in animals before Indiana University proceeded to human clinical tests. At this point in time, both Indiana University and General Foods believed we had isolated the most effective and efficacious of the phosphate compounds tested in animals. This was monosodium phosphate, a common food nutrient. Although we ran into some taste problems when this nutrient was added to cereals, we believed we could overcome them.

The 12 months of animal tests indicated that the phosphate nutrient acted systemically in animals. That is, the compound was absorbed by the body system and moved to the teeth with a strengthening effect.

When the results indicated that phosphates effectively inhibited dental caries in animals, Indiana University proposed testing them on humans. The objective, as in similar scientific research, was to determine whether the phosphates would prove as effective in stopping or slowing caries in humans as the phosphates did in laboratory animals. Ready-to-eat breakfast cereals were selected because they were widely consumed, by both adults and children, and they included both presweetened and nonsweetened cereals.

The first pilot clinical study on presweetened breakfast cereals was started by Indiana University in Bloomington, Ind., in October 1962. One group of people was given cereals enriched with phosphates at various levels. The second, or control group, received cereals without the phosphate additives. Individuals consumed the cereals as they normally did. Both Indiana University and General Foods examined the results at the end of the first 6 months and at 12 months and they were favorable. This was done before the decision was made to try further clinical tests.

After this decision was made, a second clinical test was started in South Bend, Ind., in 1963. Here presweetened and nonsweetened cereals were tested. However, the level of phosphate additives used were those we believed were most effective and which would be used when and if the products could be marketed to the public. Again, as in all clinical studies, control groups received cereals without the phosphates.

During 1964 Indiana University started four more clinical studies. In Fort Wayne, presweetened cereals enriched with phosphates were tested in an area where the community water supply was flouridated. Previous tests were in localities where the water was not flouridated.

In Goshen, Ind., the test was designed to answer several different questions. How did monosodium phosphate work on the teeth? Was it absorbed into the body system after ingestion and then recirculated back into the tooth structure? Or did it act directly on the tooth structure as soon as it entered the mouth? Several studies with laboratory animals had shown that the compound was absorbed into the system and recirculated to the teeth. Thus the Goshen study was

conducted to determine how it would work in humans. This Goshen study had a second purpose. That was to discover if other ingredients in the cereals or if a recently developed "flavor mask" (another phosphate compound) either enhanced or detracted from the effectiveness of the monosodium phosphate.

To determine if monosodium phosphate was absorbed and recirculated by the body system, one group in Goshen were given gelatin capsules which they swallowed. A second group were given chewable tablets which they chewed before each meal. Two other groups were given placebo tablets to control the study. One of these later groups was given presweetened cereals enriched with the phosphate nutrient. All other groups had presweetened cereals but without the phosphate additives.

In Muscatatuck, Ind., the study was designed to determine the effect of the monosodium phosphate nutrient on dental health if the cereals were eaten once a day under controlled supervision. In previous studies, the cereals were eaten as the individuals desired, and not necessarily every day. Presweetened cereals with and without phosphates were employed.

Finally, in 1964, the fourth clinical study was started in North Dakota. This study was done by researchers who had no connections with Indiana University so that a greater degree of objectivity could be attained for all the tests. In North Dakota, presweetened cereals with and without phosphates were used.

As a further means of assuring ourselves that this research was being conducted correctly, Indiana University and General Foods briefed the American Dental Association in August 1963 on the projects under way or planned. Then in April 1964, we gave the American Dental Association all of the Indiana University laboratory and clinical test data.

Five months later, in September 1964, General Foods filed with the U.S. Food and Drug Administration "Notices of Claimed Investigational Exemptions for a New Drug" (IND) as required by federal regulations which had just come into effect. These IND's covered the clinical research being conducted.

Now the reports that we were receiving about this clinical research continued to be favorable. The phosphate nutrients appeared to be effective in reducing the incidence of human dental caries. As I stated earlier, the laboratory animal tests indicated that the phosphate was absorbed by the body's system and recirculated to the tooth structure. This seemed to be confirmed by all the results we were getting from the clinical tests. What was more important, when used in cereals, the phosphate nutrient appeared to be mainly effective in reducing or inhibiting dental caries on the surfaces between the teeth, surfaces which cannot benefit from normal brushing. Both Indiana University and General Foods now believed with conviction that we had developed an effective method of contributing to better dental health for the population. We felt that the data we had collected now justified our asking the FDA for permission to market cereals containing the monosodium phosphate nutrient and to advertise that these products would help strengthen teeth against decay. As you know, Federal regulations require FDA approval before any such type of therapeutic claims can be made.

The FDA was given a briefing on the whole research program in November 1964. At that time, the FDA informed us that we would have to provide them with the results of 2 years' clinical tests at a minimum, an independent study on identical formulas of the additive, data on consumption of cereals, and a full tabulation of all the caries discovered during the clinical studies.

Accordingly, we worked closely with Indiana University to prepare the volumes of material required by the FDA. It took nearly 11 months to assemble all the material needed. Then in September 1965, General Foods submitted this data to the FDA as part of a New Drug Application (NDA).

Meanwhile, the successful animal work and the promising results of the clinical studies on cereals led us to start new tests on laboratory animals using other products, including a wide range of natural and synthetic acid containing sweet beverages. These animal tests, as before, were in vitro and in vivo. When they produced favorable results indicating that the phosphate nutrient was effective in mitigating the acid effect on animal tooth enamel, we felt the time had come to try clinical tests with beverages.

So, in October 1966, we filed Notices of Claimed Investigational Exemptions for a New Drug (IND) with the FDA on powdered soft drink mixes enriched with the phosphate nutrient. Clinical tests commenced in November 1966 in Elkhart, Ind. Here Indiana University used soft drinks with and without the phosphate nutrient—along with a control panel.

Then in 1967 two more clinical tests were initiated by Indiana University. One in Concord, Ind., tested an instant chocolate drink with and without the phos-

phate additive. In Peru, Ind., a different study was conducted. Here capsules and tablets containing the phosphate nutrient and placebos were tested. This was done to corroborate the earlier tests in Goshen, Ind., which indicated that capsules and tablets containing phosphate were effective in inhibiting caries. Different amounts of the phosphate were tested among different groups in Peru.

In the meantime, the FDA has not yet acted favorably on General Foods' original New Drug Application for cereals with phosphate nutrients. The FDA repeatedly requested more data and new data. This was provided as available. Then in May 1967, the FDA rejected our NDA as being "incomplete." Both General Foods and Indiana University believed that the FDA's action was based on the form of our NDA, that is, on the manner in which we presented the data.

We believed that the data itself was not under question. Indiana University worked closely with General Foods to rearrange the manner in which our data was presented in the NDA. Thus in January 1969, General Foods submitted its revised NDA to the FDA.

Mr. Chairman, it doesn't have to be said that the research road is a rocky one, piled high with obstacles and clogged with thorn bushes. Yet the rewards at the end of the path justify the efforts required to reach the end. With our revised NDA being studied by the FDA, we felt we were close to our goal.

Then suddenly, a rockslide blocked the path to us. In the summer of 1969, one of the primary clinical investigators of Indiana University raised questions about the interpretations of the clinical test results. The questions were aimed at the manner by which the X-rays and the clinical examinations had been interpreted. Abruptly, the validity of the data, especially the favorable conclusions, was now under question.

With this cloud hanging over the entire program of research, General Foods felt obligated to withdraw its New Drug Application from the FDA until we could clear up the entire situation. Therefore, with the concurrence of Indiana University, General Foods in August 1969, informed the FDA that it was voluntarily withdrawing its NDA for presweetened cereals.

To answer the questions posed, General Foods and Indiana University both reanalyzed the results of the clinical tests, utilizing outside experts to achieve the maximum objectivity and independent professional evaluation. This reanalysis was performed by experts who had not previously seen any of the research data. And this data was arranged in a random manner so that the new observers did not know what previous examiners had concluded.

As a result of their reanalysis, Indiana University concluded that certain portions of their clinical program could have been affected by an unconscious bias. It was felt that this could have been caused by the fact that the individuals examining the X-rays and the clinical examinations may have had access to the codes used to disguise the products used during the tests. Thus an unconscious bias could have affected their final conclusions which had been previously reported to the FDA in the New Drug Application.

CONCLUSIONS

As I stated earlier, in our original New Drug Application for cereals with the FDA, we reported that the laboratory animal and the clinical human tests had produced some favorable findings.

1. Monosodium phosphate when consumed in both regular and presweetened breakfast cereal was effective in reducing the incidence of human dental caries. It was particularly effective on the surfaces between the teeth where brushing did not reach.
2. Tests with phosphate capsules indicated that the phosphate was absorbed by the body, and recirculated to the tooth structure with a hening

Actually, these findi[illegible] published in the Journal of the American Dental Association in M[illegible] and March 1968.

However, the reanalysis [illegible] Indiana University and General Foods, as well as by the outside experts, ch[illegible]d the entire picture for cereals and phosphates. This reanalysis concluded the [illegible]eals enriched with monosodium phosphate produced "virtually no eff[illegible]" [illegible]ng human caries. This applied to both presweetened and nonswee[illegible]eak[illegible] cereals.

For beverages, the or[illegible]one[illegible]ons from clinical tests indicated a beneficial effect in reducing caries. [illegible] the reanalysis did not fully support these original

conclusions. The reanalysis showed some statistical trends that the phosphate additive seemed to mitigate the demineralization effect on teeth enamel believed to be caused by the presence of acids in the beverages.

As you probably know, many beverages contain acids of different kinds. For example, citric acid in citrus fruit juices, lactic acid in milk, phosphoric acid in some carbonated soft drinks, and other acids in other natural fruit juices. There is much evidence that the acid in natural fruit juices dissolves some of the minerals in the enamel of the teeth. And as I said earlier, the use of phosphates in the beverages tested indicated some mitigration of this demineralization action.

Action Taken by General Foods

Now let me tell you about the actions taken by General Foods. All of the testing by Indiana University had used the nutrient monosodium phosphate as the active ingredient. As I just said, it appeared to have some effect on the demineralization caused by the acid in the beverages. Therefore, General Foods decided to add monosodium phosphate to those powdered soft drink beverages it had been testing. After we had overcome some taste problems caused by the use of this compound in the beverages, we started adding monosodium phosphate to our powdered beverages in 1969, 1970, and 1971.

Let me say here that despite 10 frustrating years down a largely unproductive path, General Foods did not stop research aimed at improving the nutritional content of our products and their effects on dental health. We therefore continued laboratory work on animals, seeking the effectiveness of other nutrients in beverages. We discovered another phosphate which appeared to be more effective than monosodium phosphate in counteracting the effect of acid on teeth enamel. This compound is called monocalcium phosphate. In our animal studies, laboratory rats consuming a soft drink enriched with monocalcium phosphate showed less demineralization and often less cavities than rats consuming natural fruit juices.

Both calcium and phosphorus are required mineral nutrients needed by man. The human body contains both calcium and phosphorus. Most of the body's calcium is found in the bones, although the mineral has roles in many other functions of the body. For example, calcium plays a role in cell permeability, in muscular mechanisms, and is vital to the development and maintenance of healthy teeth.

The human requirement for calcium varies from about 400 mg. per day for an infant up to as much as 1400 mg. per day for teenage boys. An average young adult male requires about 1000 mg. per day of calcium.

Numerous dietary and health surveys have indicated that many individual diets are lacking in calcium. The 1965 U.S. Department of Agriculture dietary survey reported that calcium and iron were the nutrients most often found below dietary requirements. This is usually attributed to insufficient ingestion of milk and milk-derived products. Our own summary of many dietary surveys reported in medical and scientific journals show that calcium is very often lacking in the daily diet.

Consistent with these dietary needs and in light of the favorable animal studies, we have been enriching our powdered beverages with the nutrient monocalcium phosphate since 1972. These are the products that are now on the market. The monocalcium phosphate has replaced the monosodium phosphate added in 1970–71.

I want to emphasize here and now that we are *not* making any claims that monocalcium phosphate will inhibit human caries. We just don't know. But it is a well-known nutrient and it is needed in the diet.

In the meantime, General Foods continues laboratory explorations of many different nutrient compounds, seeking to further improve our products.

Senator Percy. Well, we thank you very much.

I have a few very short questions, and with some brief answers on your part we can get out of here in just a few minutes. However, if you do want to amplify your comments in any way we will certainly see that they are inserted in the record.

Would you have in mind any kind of a figure for the amount of money that General Foods has spent in this research over the period of 13 or 14 years?

Mr. CLAUSI. Senator Percy, I can only give you the figure that we have been able to identify via specific project costs both in and out of Indiana University funding, and this is in the neighborhood of $1½ million.

Senator PERCY. I suppose the slogan goes in advertising, half of the money is wasted. The trouble is to find out which half. My own experience in research is that probably far more money than 50 percent is spent on nonproductive research. But that is the nature of the business. It is highly risky.

If you spent $1½ million in this field do you feel as research goes it has been cost effective and that you received some results which now will be satisfying to General Foods as well as to the general public?

Mr. CLAUSI. Well, obviously we would at this point have preferred not to have gone through the largely unproductive human clinical work. However, if we are correct on the basis of our own laboratory observations and dietary surveys that the addition of monocalcium phosphate nutrients to our beverage products has in effect made them more nutritious for the general public then we think that is money well spent.

Senator PERCY. It has been assumed by some that the rationale that must have been used initially for the phosphate studies was the belief held by some that the increasing consumption of presweetened cereals was probably going to result in dental problems. Is this true in your judgment?

PUBLIC ANXIETY OVER INCREASED CONSUMPTION

Mr. CLAUSI. I think there was very much being said at various dental association meetings, certainly by dentists to patients; sufficient, let's say, to create public anxiety about sugar-containing foods in general, presweetened being one. We felt that there would certainly be a receptivity to the idea of a better presweetened product.

But I would like to come back and reemphasize the point that the reason that ready-to-eat cereals were selected, the primary reason was because they were believed to be the most ideal vehicle for delivering this type of agent to the age group and the economic strata that could use it.

Senator PERCY. Do you agree or disagree with Dr. Gilkes' evaluation of your second study comparing presweetened cereals with regular cereals that presweetened cereals tend to cause more cavities?

Mr. CLAUSI. I can say that our statistical evaluation within that test, and the only test, although it wasn't designed to explore this difference, from which you could draw such conclusions that our statistical analysis showed no significant difference between presweetened and non-presweetened panels in terms of caries incidence. No significant difference.

Senator PERCY. For the record again, then is it your opinion after reviewing all the available scientific evidence that the presence of phosphates in the diet acts to reduce the incidence of tooth decay which may result from the consumption of presweetened cereals?

Mr. CLAUSI. I would like, if you would, to please repeat that question because I think there are some subtle nuances here in the way I answer you.

Senator PERCY. The question is, is it your opinion after reviewing all of the available scientific evidence that you have accumulated and others may have accumulated—and certainly you are familiar with other experimentation that has been done in this area—that the presence of phosphate in the diet acts to reduce the incidence of tooth decay which may result from the consumption of presweetened cereals?

Mr. CLAUSI. I would have to say that I have no way of having an opinion that the use of phosphates in the diet will have that effect. I can only say that in our opinion there are some encouraging findings based on animal studies that the use of monocalcium phosphate in acid sweetened beverages can mitigate against the enamel erosion which can be a forerunner of caries and possibly might have some beneficial effect on caries reduction. But that would all have to be confirmed by human clinical work of the type I described earlier, very laborious, very complicated, and very difficult to control.

Senator PERCY. Could we turn to beverages then and give us your opinion as to whether certain beverages do tend to cause tooth decay in humans.

Mr. CLAUSI. Again I can't comment on the effect in humans. I can say, though, on the basis of laboratory animal studies that acid—and I stress the word acid—sweetened beverages, both natural and synthetic, have an erosive effect on the teeth, and also under conditions of test can be shown to induce more caries than, let's say, water, plain water control. But the caries effects are less clear than the erosion effects.

Senator PERCY. What, in your view, is the culprit in the beverage?

Mr. CLAUSI. Our view is it very likely is the acid more than the sugar, although the combination of the two may have some synergy. There may be some synergistic effect between the two.

Senator PERCY. I will put the same question again on the addition of phosphate. If phosphate is added to the beverage is this a satisfactory way to eliminate or reduce their tendency to cause tooth decay?

"COULD" HAVE MITIGATING EFFECT

Mr. CLAUSI. I would rather state my position this way, Senator, if I may; that we believe that the addition of calcium phosphate—that is a combination nutrient, calcium and phosphorous—to acid sweetened beverages, both natural and synthetic, could have a mitigating effect against the tooth enamel erosion tendency of these products. We feel we have confirmed that in animals to our satisfaction. Hence the addition to our products.

Senator PERCY. That is since 1972?

Mr. CLAUSI. Yes.

Senator PERCY. You were here in the hearing room when I asked Dr. Tepper to state the criteria that he would lay down so that a claim can be made. Do you feel that you have met those criteria now?

Mr. CLAUSI. Senator, I would like to stress that we are not making a claim.

Senator PERCY. I see.

Mr. CLAUSI. We are adding two known nutrients, one of which very recently has come very much into the limelight as being one of the borderline deficient nutrients in our modern diet. We feel we are building better products. We are not making any claims, and we will not make claims until we conform to Food and Drug's criteria, of course.

Senator PERCY. Well, I think it is very important that you do make that clear, and it is not inconsistent with the company's policy, as I have understood it to be very conservative in claims and to try to back up claims with exhaustive research.

Just one question with respect to your testimony that I would like clarification. In your statement you said questions were raised about the data. What data were involved and what questions were raised?

Mr. CLAUSI. The questions were raised primarily about the data that had been accumulated in the two test cities in which this primary investigator who raised the question had participated as one of the examiners. These were Bloomington, Ind., and South Bend, Ind. So those two tests in particular, since they were the ones that this examiner was involved in, were the subject of question, although the ramifications obviously went beyond those two tests since essentially the same procedures had been used by the clinical investigators throughout.

Senator PERCY. I have no further questions. Mr. Schlossberg, do you have any questions?

EVALUATION OF STUDIES STATE FINDINGS ACCURATE

Mr. SCHLOSSBERG. There is one point that slightly confuses me; it has to do with the question regarding the accuracy of the data and the use of independent evaluators.

As I understand it, back in 1966, General Foods had two independent researchers evaluate the studies and submit an independent evaluation to the agency regarding the format of the studies and the accuracy of the findings. Do you know which letter I am referring to?

Mr. CLAUSI. Yes, I do.

Mr. SCHLOSSBERG. Those two independent researchers, Dr. Grizzel and Dr. Smith, determined: That, in their opinions, the studies had been well formulated, well conducted, and the findings were accurate.

Mr. CLAUSI. Yes. I can see your confusion, and let me clarify that. Again remember this is all prior to the question being raised by the primary investigator concerning the way the protocol had been carried out. Therefore the independent judgments to which you are referring were those that examined the protocols, the layout of the test, the design of the test, the statistical accuracy of it, but all, of course, on the assumption that there was no bias, indirect or direct, that the protocols had been adhered to as written. It wasn't until one of the people actually involved in the test raised the issue of how the test was carried out that we were aware of the challenge to the data. Prior to that time things appeared to be in order.

Mr. SCHLOSSBERG. One more question: Because of the adding of the monocalcium phosphate you removed the fumaric acid in Tang and Kool-Aid—why was that done?

Mr. CLAUSI. We have always used citric acid in Tang, but about a year ago we went to citric acid in Kool-Aid also. This had really nothing to do with the subject that we are discussing here today. There were at that time some questions being raised by the World Health Organization over the daily intake, the advisable daily intake of fumaric acid, and the point was that perhaps too much fumaric acid is being consumed. So it was on the basis of that question being raised and our desire to be helpful and manufacture as safe a product as we can that we switched our formula to citric acid. It really had nothing to do with this issue.

Mr. SCHLOSSBERG. I have no further questions.

Senator PERCY. I think the hearings today have shown the great difficulty in getting data that reasonable men can agree on in the field of food and diet and nutrition. We certainly have a great need for a certain body of basic research to get a fundamental basis from which we can proceed.

But we are very grateful for your appearance, for the work that went into the preparation of this material, and the testimony that was given, and for FDA's participation also. Thank you very much.

The committee is in recess, to reconvene at the call of the Chair.

(Whereupon, at 12 o'clock noon, the Select Committee was recessed.)

APPENDIX

ITEMS PERTINENT TO THE HEARING

AUGUST 21, 1969.

GENERAL FOODS CORP.,
White Plains, N.Y.
(Attention of Dr. B. F. Daubert.)

GENTLEMEN: Reference is made to your new drug application dated September 30, 1965 pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation "Post Alpha-Bits, Post Crispy Critters, Post Sugar Crisp, Post Sugar Sparkled Rice Krinkels, and Post Sugar Sparkled Flakes, with Nutrident (Monosodium Dihydrogen Phosphate)".

We also acknowledge receipt of your additional communications dated February 12, 1969 and August 14, 1969 respectively.

Although it is not necessary for the application to be withdrawn since it remains inadequate as stated in our letter of May 19, 1967, in compliance with your request the application is regarded as withdrawn. In accord with section 130.8 of the regulations under the Federal Food, Drug, and Cosmetic Act, the withdrawal does not prejudice any future filing of the application. You may request that the information you have withdrawn be considered in connection with any resubmission.

Sincerely yours,

JOHN JENNINGS, M.D.,
Acting Director, Bureau of Medicine.

GENERAL FOODS CORP.,
White Plains, N.Y., June 4, 1970.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
Food And Drug Administration,
Washington, D.C.
(Attention of Dr. Frederick J. Grigsby.)

GENTLEMEN: Relative to 21 CRF Sec. 130.3 (a)(5) attached are Yearly Progress Reports concerning the Dental Caries Clinical Studies being carried out under the following IND's 3636, 3637, 3638, 3712, 3778, 3845 and 3979.

Also attached is a letter dated March 11, 1970 from Dr. Simon Katz to Dr. Joseph C. Muhler of the Indiana University Preventive Dentistry Research Institute. *Dr. Katz is the investigator in the studies conducted under IND's 3636, 3637,* 3638, *3712* and 3845. *This letter indicates Dr. Katz's conclusion that the beverage products used in certain of the studies cause a higher incidence of caries and that the same products with the additives have a lower incidence of caries.* General Foods, the sponsor, has not completed its review of these studies, but has elected to resolve any doubt with respect to the caries problem stated in Dr. Katz's letter by improving the soft drink mix product used in IND 3636 and similar soft drink mix products *by the placement of the additive in its current production of the products without making any claims for effectiveness of the additive. The labels for the products are attached showing the presence of the additive. Consideration is being given to the addition of the additive to other beverage mix products being marketed by sponsor which are similar to the one used in IND 3712.* Products involved in IND's 3637, 3638 and 3845 or products similar to them are not currently being marketed by General Foods.

Very truly yours,

Dr. K. G DYKSTRA,
Director of Nutrition.

INDIANA UNIVERSITY AT INDIANAPOLIS,
Indianapolis, Ind., March 11, 1970.

Dr. JOSEPH C. MUHLER,
Preventive Dentistry Research Institute,
Indianapolis, Ind.

DEAR DR. MUHLER: I have recently completed the three year examination of the children who participated in the Elkhart Study. Since this examination completes the study, I would like to make the following statements:

1. No side effects (on general health) attributable to the products under test were observed by me, nor were they reported by teachers, parents and/or children.

2. However, the tabulation of the 24-month examination data, analyzed after my last report, shows a significant increase of dental caries in children pertaining to Groups 1 and 3 with regard to the water topical control, i.e., Group 7 (Table I). Dr. A. L. Russell, an independent investigator has arrived at the same conclusion after evaluating the 24-month clinical examination original forms. There is also a numerically important increase of dental caries in children from Groups 8 and 9 in comparison to Group 7 (Table II). The statistical significance of this effect is being currently analyzed.

3. Several local dentists have expressed their concern to me that there is a cariogenic effect on (one or more) of the products under test. This concern is based upon their findings of what appears to be an increased dental caries rate and an increase in demineralization of pre-carious lesions in some of their patients who were at that time participating in the study.

4. In view of the situation mentioned in points 2 and 3 above, I decided to review the whole study again, retabulating all the examination sheets since the 12-month examination period. This retabulation was conducted separately for the clinically observed (chiefly pit and fissure caries) and radiographically diagnosed lesions (smooth surface caries). Lesions diagnosed both clinically and radiographically were not compounded. In all these instances the clinical data were given precedence. The reason for this procedure is that recent scientific evidence strongly suggests that these two types of lesions are etiologically different, so that the effect on one of them may, in some instances, be independent from the effect on the other.

5. I have retabulated Groups 1, 2, 3, 4, and 7 for clinical evidence at 12-months; and Groups 1, 2, and 7 for x-ray evidence at 12-months and clinical evidence at the 18-month examination. The remaining groups are being retabulated at the present time.

6. The results at present can be summarized as follows:

12-Month Retabulation. Clinical Data (Tables III and IV)

(*a*) *The products used in Groups 1 and 3 (regular and presweetened Kool-Aid) are markedly cariogenic in comparison to the water topical control (Group 7, Table III).*

(*b*) The addition of sodium dihydrogen phosphate cancels-out this cariogenic effect (Table III).

12-Month Examination. X-Ray Data. (Tables III and IV)

(*c*) The x-ray data show no important difference between the groups, and thus their addition does not modify the picture described in a and b above. It would seem that the cariogenic effect of Kool-Aid occurs mainly in pit and fissure lesions, which are diagnosed clinically.

18-Month Examination. Clinical Data (Table V)

(*d*) *Table V which shows these data, indicates that Kool-Aid is decidedly cariogenic, and that the addition of phosphate cancels-out this effect.*

7. These findings clearly indicate that several of the products used in the Elkhart Study are definitely cariogenic, and that a solution for that problem has been found. Therefore, I would like to propose that, in order to discharge our professional, ethical, and moral responsibilities to the public the information presented in this report be submitted to the sponsor and then to the American Dental Association.

Sincerely,

SIMON KATZ, D.D.S., Ph. D.,
Assistant Professor of Preventive Dentistry.

TABLE I.—STATISTICAL EVALUATION OF ELKHART STUDY DATA AT 2 YEARS (CLINICAL AND RADIOGRAPHIC) (DR. KATZ' DATA)

Groups and Increments compared	Increment	Percent difference	"t" value	Probability
vs 2:				
DMFT	2.80±0.22 versus 2.46±0.19	12.2	1.171	[1] 0.250
DMFS	5.20± .42 versus 4.27± .37	17.9	1.660	[1] .098
IPS	2.45± .31 versus 1.90± .28	22.4	1.334	[1] .186
vs 7:				
DMFT	2.80± .22 versus 2.17± .19	29.0	2.174	.031
DMFS	5.20± .42 versus 3.93± .33	32.4	2.384	.019
IPS	2.45± .31 versus 1.77± .20	38.4	1.857	[1] .066
vs 7:				
DMFT	2.46± .19 versus 2.17± .19	13.4	1.082	[1] .291
DMFS	4.27± .37 versus 3.93± .33	8.6	.682	[1] .496
IPS	1.90± .28 versus 1.77± .20	7.3	.377	>[1] .500
vs 4:				
DMFT	2.91± .19 versus 2.81± .20	3.4	.360	>[1] .500
DMFS	5.15± .36 versus 4.63± .37	10.1	1.015	[1] .321
IPS	2.15± .25 versus 2.20± .27	2.3	.164	>[1] .500
vs 7:				
DMFT	2.91± .19 versus 2.17± .19	34.1	2.754	.006
DMFS	5.15± .36 versus 3.93± .33	31.0	2.493	.014
IPS	2.15± .25 versus 1.77± .20	21.5	1.181	[1] .246
vs 7:				
DMFT	2.81± .20 versus 2.17± .19	29.5	2.329	.021
DMFS	4.63± .37 versus 3.93± .33	17.8	1.396	[1] .169
IPS	2.20± .27 versus 1.77± .20	24.3	1.289	[1] .198
and 3 vs and 4:				
DMFT	2.85± .14 versus 2.63± .14	7.7	1.110	[1] .278
DMFS	5.18± .28 versus 4.45± .26	14.1	1.931	.055
IPS	2.30± .20 versus 2.05± .19	10.9	.924	[1] .362

[1] N.S.

TABLE II.—ELKHART STUDY—DMFT AND DMFS AFTER 24 MONTHS (DR. KATZ' CLINICAL AND X-RAY DATA)

Group	Average Δ DMFT	Average Δ DMFS
1	2.80	5.20
2	2.46	4.27
[illegible]	2.91	5.15
[illegible]	2.81	4.63
5	2.53	4.46
6	2.73	4.68
7	2.17	3.93
8	2.67	5.21
9	2.62	4.95

TABLE III.—ELKHART STUDY—CARIES INCREMENTS AT 12 MONTHS—CLINICAL AND X-RAY DATA (DR. KATZ' DATA)

Group	Clinical examination ΔT	Clinical examination ΔS	X-rays ΔT	X-rays ΔS	Percent ΔS differences with group 7: Clinical	Percent ΔS differences with group 7: X-ray
1	0.46	0.46	0.34	0.68	----------	----------
2	.87	1.27	.32	.69	+176.08	+1.5
3	.40	.37	.41	.86	−19.5	+26.5

[1] + means more caries than group 7; − means less caries than group 7.

Note: Extracted teeth are not included in this table.

TABLE IV.—ELKHART STUDY, CARIES INCREMENTS AT 12 MONTHS—CLINICAL DATA

Group	N	ΔDFT	ΔDFS	Difference with group 7 ΔDFT	Difference with group 7 ΔDFS
1	173	0.46	0.46		
2	175	.87	1.27	+89.13	+176.08
3	198	.40	.37	−13.04	−19.56
4	166	.87	1.02	+89.13	+121.74
5	188	.52	.57	+13.04	+23.91

Note: Extracted teeth are not included in this table.

TABLE V.—ELKHART STUDY, CARIES INCREMENTS AT 18 MONTHS—CLINICAL DATA ONLY

Group	N	ΔDFT	ΔDFS	Difference with group 7 (in percent) ΔDFT	Difference with group 7 (in percent) ΔDFS
1	189	1.20	1.63		
2	165	1.41	2.45	+17.2	+50.3
3	185	1.31	1.57	+9.2	−3.7

Note: Extracted teeth are not included in this table.

GENERAL FOODS CORP.,
LAW DEPARTMENT,
May 24, 1971.

DR. WILLIAM J. GYARFAS,
Division of Surgical and Dental Drug Products, Office of Scientific Evaluation, Bureau of Drugs, Food and Drug Administration, Rockville, Md.

DEAR DR. GYARFAS: At our May 3 meeting certain commitments were made and points of view expressed which I believe it would be appropriate to confirm at this time. Also I would like to bring you up to date on related developments.

Prior to the receipt of your letters of March 15 requesting the submission of data, pursuant to Section 103.3(a)5 of the *New Drug Regulations*, General Foods was of the belief that it had fully complied with its obligations with respect to the submission of data and other information in connection with the INDs. This belief was based on the wording of that Section, which reads in part—"Upon request of an identifiable, trained and properly authorized employee of the Department, at reasonable times, these reports shall be made available for inspection, and on written request copies of these reports shall be submitted to the Food and Drug Administration". To the best of our knowledge, the letters dated March 15 constitute the first written request for such reports and at our May 9 meeting it was decided that the data in the form of copies of the examination sheets would be submitted.

General Foods committed itself to the submission of all of the examination sheets by the end of the month of May. The work involved in fulfilling this commitment is well under way and every effort is being made to meet the deadline. However, it should be pointed out that the job is not as simple as we originally thought. The examination sheets contain entries made by the original examiner (Dr. Katz) and a second examiner (Mr. Stookey). Their respective entries were made in different colors so that they could be readily identified as to source. Unfortunately, the difference in color is lost when photocopies are made. Therefore, it was necessary to go through each examination sheet and mark the entries in a distinctive manner which would be picked up when photocopying the records. This added step has obviously taken a lot of time not orginally contemplated.

Shortly before the end of the month we will hand deliver to FDA's mailroom the data (examination sheets) we have completed copying. These will be bound in volumes, with separate volumes for each IND, identified with the IND number. At the same time these are delivered, I would appreciate the opportunity to meet with you to show you samples of the type of records being submitted. This will enable you to be aware of what has been done and to give us any guidance you feel is appropriate so that we can be as certain as possible that we are fully complying with your March 15 request.

General Foods disagrees strongly with the position taken by Food & Drug that the presence of sodium phosphate in acid containing beverages such as KOOL-AID soft drink mix and TANG instant breakfast drink can constitute some sort of therapeutic claim for this ingredient. Be assured General Foods has no intention of making any claim with respect to this ingredient. However, we believe we should formulate products in keeping with the latest scientific knowledge, particularly when there is some indication of a possible elimination of an adverse effect. General Foods is currently evaluating acid systems which use other ingredients and which have been shown by laboratory tests to do a better job of modifying or inhibiting the effect acid might otherwise have. We will keep you informed on our efforts in this area, but it should be clearly understood that our submission of information with respect to this is not to be considered an admission on our part that the inclusion of such a modified acid system is in any way a drug.

General Foods stated its position that it was willing for Food & Drug to release any information filed with Food & Drug by General Foods concerning the studies conducted by Indiana University under General Foods' sponsorship. Also the only reason why General Foods is hesitant to release any such information is due to the position taken by Food & Drug that any publicity resulting from the release of any information might be construed by Food & Drug as the making of a therepeutic claim which might result in Food & Drug having to take some action with respect to General Foods products which contain mono sodium dihydrogen phosphate.

During our May 3 meeting there was considerable discussion with respect to releasing information to the Federal Trade Commission and the staff of Senator Edward Kennedy. On May 6 General Foods representatives met with Mr. Bates of Senator Kennedy's office and explained to him the situation with respect to release of any information concerning the beverage work. We told Mr. Bates that though we were willing to give him the information in the form of the Indiana University manuscripts, we were reluctant to do so in view of FDA's position that any publicity might be considered the making of a therapeutic claim for an unapproved drug. We concluded by suggesting that it might be appropriate to have a meeting with representatives of Senator Kennedy's office, Food & Drug and General Foods present so that there would be a fuller understanding of this situation and we could avoid or minimize any problems involved. Mr. Bates seemed to approve of this idea and I understand he has been in contact with Mr. Anderson. I also understand that any such meeting will not take place until Senator Kennedy's letter has been answered by Food & Drug and then only if it still appears appropriate to have such a meeting.

In connection with the two manuscripts left with you at our May 3 meeting, it should be understood that these are the work of Indiana University. General Foods does not necessarily agree or disagree with the findings set forth in the manuscripts. We are in the process of drawing our own conclusions with respect to the work and will include such conclusions in the monitor report you have requested.

We understand that Indiana University has submitted their manuscripts for publication in the *Journal of Dental Research*, as permitted under Section 130.3(a) 10 of the *New Drug Regulations*.

Please be assured of General Foods' cooperation in trying to resolve any problems involved in this rather complex situation. We appreciate the cooperation Food & Drug has given us thus far.

Yours truly,

GORDON R. BROWN,
Attorney.

OFFICE OF SCIENTIFIC EVALUATION,
BUREAU OF DRUGS,
March 15, 1971.

GENERAL FOODS CORP.
White Plains, N.Y.
(Attention of Dr. K. C. Dykstra.)

GENTLEMEN: Reference is made to your discontinued Notice of Claimed Investigational Exemption for a New Drug for Monosodium Dihydrogenphosphate Incorporated into an Orange Flavored Breakfast Drink for the Purpose of Inhibiting Dental Caries, IND 3712, submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act.

Section 130.3(a)(5) of the New Drug Regulations requires that the sponsor submit accurate progress reports of the investigations and significant findings pertaining to safety and effectiveness of the drug. Your submission in this regard are inadequate.

Please submit final reports and data from each investigation and a summary of your evaluation as to the safety and effectiveness of this drug.

Your prompt attention and response to this letter will be appreciated.

Sincerely yours,

WILLIAM J. GYARFAS, M.D.,
Director, Division of Surgical-Dental Drug Products.

DENTAL OFFICER SUMMARY FOR IND 3712

AUGUST 8, 1967.

Name of Sponsor: General Foods Corp., White Plains, New York 10602.

I. DESCRIPTIVE DATA

1. Name of Drug:
   Trade Name: Monosodium dihydrogen phosphate incorporated into an orange flavored breakfast drink mix for the purpose of inhibiting dental caries.
   Generic Name: None.
2. Proposed Uses: As anticaries agent.
3. Chemical Name and Formula: Monosodium dihydrogen phosphate; NaH_2PO_4.
4. Mode of Action: None given.
5. Formulations, route of Administration and Dosage: Monosodium dihydrogen phosphate incorporated into an orange flavored breakfast drink; Orally; No specific dosage recommended.
6. Related drugs:
   IND 2148—NaH_2PO_4 added to 5 cereals, General Foods Corp.
   IND 2518—Experimental Dentifrice T-8 (toothpaste), Lever Brothers Co.
   IND 2833—Prophylaxis Paste, Bristol-Myers Co.
   IND 2954—0.75% Monosodium Phosphate added to various cereals, Kellogg Co.
   IND 3636—1.2 gm. Monosodium Dihydrogen Phosphate incorporated into seven non carbonated flavored instant soft drink mixes for the purpose of inhibiting dental caries, General Food Corp.
   IND 3638—0.78 gm. Monosodium Dihydrogen Phosphate incorporated into a low calorie sweetening powder for the purpose of inhibiting dental caries, General Foods Corp.
   IND 3778—Monosodium Dihydrogen Phosphate incorporated into a chocolate flavored beverage mix for the purpose of inhibiting dental caries, General Foods Corp.
   IND 3845—Monosodium Dihydrogen Phosphate incorporated into an instant breakfast mix for the purpose of inhibiting dental caries, General Foods Corp.
   IND 3637—1.2 gm. Monosodium Dihydrogen Phosphate incorporated into 7 non carbonated artificially sweetened instant soft drink mixes for the purpose of inhibiting dental caries, General Food Corp.
   IND 3979—Monosodium Dihydrogen Phosphate incorporated into tablets and/or gelatin capsules for the purpose of inhibiting dental caries, General Foods Corp.
   NDA 16-330—(Incomplete) Monosodium Dihydrogen Phosphate incorporated into five pre-sweetened breakfast cereals for the purpose of inhibiting dental caries, General Foods Corp.

II. MANUFACTURING CONTROLS REVIEW

"Remarks: For phase III, the flavor ingredients should be identified.
Conclusions:
Controls unsatisfactory. Sponsor should be requested to clarify the specifications, identity determination and assay of the NDS in the product.
Labels lack notation of active ingredient, quantity, and caution statement."

III. PHARMACOLOGY DATA REVIEW

"Evaluation: Preclinical animal studies, an extensive bibliography and a reprint of the *Federal Register* concerning the use of phosphate have been submitted and reviewed in the pharmacology reviews of IND 2148 and NDA 16-330.

The following studies have been performed by the sponsor:

(1) Enamel Solubility Studies with Phosphates Using *in-vivo* and *in-vitro* Procedures.
(2) Dental Caries Studies in Rats and Hamsters.
(3) Enamel Solubility and Dental Caries Studies in Animals Involving Pre- and Post-natal Phosphate Administration.
(4) Plaque pH Studies Using Phosphates.
(5) Preclinical Investigations on Experimental Animals Using Phosphate Enriched-Cereals.
(6) Studies on the Function of the Salivary Glands.

Reviews of animal studies in IND 2148 and NDA 16-330 may be used as cross references to this IND.

Inasmuch as monosodium dihydrogenphosphate in GRAS as a food additive and the animal toxicity data appear to be adequate, we have no objection to having the sponsor continue clinical trials."

IV. CLINICAL INVESTIGATIONS

This clinical study was carried out simultaneously with the clinical studies of IND 3636 (Regular Kool-Aid), IND 3637 (Artificially Presweetened Kool-Aid) and IND 3638 (A Low Calorie Sweetening Powder).

A. There were two clinical investigators listed:
Joseph C. Muhler, D.D.S.
Simon Katz, D.D.S.

B. 250 children residing in an area having a water supply containing less than 0.2 ppm of fluoride were given a clinical examination with the aid of 5-7 bitewing radiographs.

C. The age range was 6-15 years. There was no distribution by chronological age or by sex. The children were divided into experimental groups according to *dental age* and past caries experience. The groups and their products were as follows:
Group I—Regular Kool-Aid
Group II—Regular Kool-Aid containing NaH_2PO_4 (IND 3636)
Group III—Artificially presweetened Kool-Aid
Group IV—Artificially presweetened Kool-Aid containing NaH_2PO_4 (IND 3637)
Group V—Artificial sweetening agent containing NaH_2PO_4
Group VI—Artificial sweetener
Group VII—Orange flavored breakfast drink mix containing 280 mg. of NaH_2PO_4 per serving.

D. The submission stated: "Although no attempt will be made to regulate consumption, an accurate consumption record, patterned after those employed in previous clinical studies, will be maintained on each subject. Additional supplies of the product will be provided on a monthly basis".

E. There are no results reported to date.

V. EVALUATION

A. The design of the studies neglected to give any consideration to the following:

(1) Previous fluoride exposure.
(2) Specific diets of subjects—hence the exact amount of phosphate ingested was not given.
(3) Better controls would have been a group that did not consume any of the products at all.
(4) No attempt was made to explain the possible mode of action of the monosodium dihydrogen phosphate.
(5) There was no mention of metabolic studies
(6) There was no exact calculated related dosage.

(7) The amount of phosphate added seems very small compared to the phosphate content of the natural diets of human beings.
(8) There was no consideration or mention of the many variables which might have a bearing on these clinical studies, such as overall oral hygiene or composition of bacterial flora of the oral cavity.

VI. RECOMMENDATIONS

A. Sponsor should be advised that these studies have defects similar to those which were pointed out at the conference June 1, 1967 on their "incomplete" NDA 16-330.
B. Sponsor should be requested to supply:
1. Identification of flavor ingredients.
2. Clarification of the specifications, identity determination and assay of the NDS in the product.
3. Identification and amount of the active ingredient and the proper caution legend on the immediate package label.

CLARENCE C. GILKES, D.D.S.

MEMORANDUM OF CONFERENCE

APRIL 7, 1971.

Present:
Gordon Brown, Attorney, General Foods Corporation, White Plains, N.Y. 10602
Marion Finkel, M.D., Deputy Director, Bureau of Drugs
Marvin Seife, M.D., Acting Director, OSE Division of Surgical-Dental Drug Products, OSE/BD-160
William J. Gyarfas, M.D., Director
Frederick J. Grigsby, M.D., Deputy Director
Clarence C. Gilkes, D.D.S., Dental Officer

Subject: IND's for which letters were written to the sponsor, dated March 15, 1971, (Monosodium dihydrogen phosphate added to various foods).

Atty. Brown opened the conference by stating that he wanted to discuss our letters dated March 15, 1971, requesting complete progress reports on the IND's which have been discontinued and he also wished to inquire about the letter from Dr. Simmons signed by Dr. Finkel on IND 2148. He continued that he had met with Dr. Jennings and had explained the work done at Indiana University and they were trying to resolve their problems associated with their cereal studies, IND 2148 and NDA 16-330. The NDA had been withdrawn because of the problems at Indiana University and they promised Dr. Jennings that they would return and give him a full report on all of the re-evaluations.

Our visitor was reminded that full reports on the re-evaluation should be submitted to the IND and NDA under which the studies were conducted.

Atty. Brown was asked who was doing the re-evaluations? He replied that Indiana University was doing them.

He was reminded that the investigator involved in the problem was on the staff at Indiana University.

The question was asked about the outside consultant who was mentioned to re-evaluate?

Atty. Brown stated that they were having an outside consultant participate in the re-evaluation.

The conversation then was directed to the discontinued IND's.

Atty. Brown stated that the reason final reports were not in was that even though the 3 year studies were completed, analysis of the x-rays and other data had not been completed and the reason for this was man power shortage at Indiana University. He added that there is some doubt that the 3 year data is valid because of the large drop out rate and decreased use of the product during the last 2 years of the study. He also added that at this time they have no intention of filing an NDA for any of the products in the IND's which were discontinued.

Dr. Gyarfas summarized that the work on the NDA began in 1964, but until this date not all of the data has been submitted. The material was found to be incomplete and the sponsor withdrew and resubmitted, and again the NDA was approvable and again the sponsor withdrew the application. He added that all data on the discontinued IND's would have to be submitted whether the

sponsor thinks it is valid or not. Also there are several investigators involved in the IND's that are not accounted for and according to the regulations they must be.

The discussion turned to the sponsor now listing monosodium dihydrogen phosphate on the package of "Kool Aid" but not making any claims.

Atty. Brown stated that the reason they were doing this was because one of the studies showed that the "Kool Aid" group came up with more cavities than the group which did not drink any beverage and so the ingredient was added to offset the erosion effect of the acid or of the beverage itself. He added that he thought someone here at FDA told them that if the ingredient was so good, to go ahead and add some but don't make any claims.

Dr. Seife stated that there must have been some misunderstanding about that point because this just can't be done.

Our visitor was told that even though monosodium dihydrogen phosphate was a GRAS item (generally recognized as safe) that the sponsor should be adding the ingredient, even to a food, for a reason.

Dr. Finkel explained to Atty. Brown that addition of this ingredient is implying a therapeutic effect and even though no statement is made it is considered a drug. She added that there has been considerable information in the literature and available to the public that caries studies have been conducted with this as the active ingredient.

Atty. Brown said he was surprised to hear this point of view and would convey same to the sponsor.

It was re-emphasized that we have no information whatsoever on the results of the "Kool Aid" studies and that there is no question of safety, but of efficacy. These studies have generated widespread inquiries all the way to the level of the U.S. Senate and we are unable to give any answers because we have no data of any kind on these studies.

Atty. Brown thanked us for our time and promised Dr. Gyarfas that they would reply to our recent letters telling us exactly when they will get the data containing the final results into us.

It was requested that the information on the Goshen, Indiana cereal study which was presented to Dr. Jennings, be submitted to IND 2148 and NDA 16-330.

The conference ended with the usual amenities at 10:20 a.m.

CLARENCE C. GILKES, D.D.S.

MEMORANDUM OF CONFERENCE

MAY 3, 1971.

Present:

Gordon R. Brown, Counsel for General Foods Corporation.
Dr. Kenneth G. Dykstra, Director of Nutrition, General Foods Corporation.
Julius Ozick, D.D.K., Consultant-General Foods Corporation.
Division of Surgical-Dental Drug Products:
William J. Gyarfas, M.D., Director.
Frederick J. Grigsby, M.D., Deputy Director.
Robert Anderson, General Counsel's Office.
Clarence C. Gilkes, D.D.S., Dental Officer.

Mr. Brown opened the conference by stating that Indiana University was used as the center of General Foods Corporation cereal studies with phosphates, and then they switched to studies of beverages with phosphates in them. He added that the principle beverage work was done at Elkhart, Indiana, and this work had been completed. He also mentioned a letter from Dr. Katz to Dr. Muhler referring to an erosion effect of the acid in "Kool-Aid" on the enamel of teeth of subjects in the study. Sodium dihydrogen phosphate (NaH_2PO_4) appeared to overcome this erosion effect and has been added to "Kool-Aid" and will soon be added to "Tang", their orange-flavored beverage mix. The effect of NaH_2PO_4 is to buffer the acid in the product. However, they were not making any therapeutic claims for the product.

There was considerable discussion of the fact that as a result of the Elkhart, Indiana, beverage studies, the sponsor proceeded to add sodium dehydrogen phosphate to "Kool-Aid" as an ingredient—making no claims—but had done so as a direct result of findings they had observed in a study conducted under IND 3636 *without submitting any of the data to FDA for evaluation.* They had taken the stand that it was a GRAS item and were adding it to buffer the acid.

Mr. Anderson stated that depending on consumer response the possibility of other complications in the future, FDA may have to take another look at this particular product.

Dr. Gyarfas stated that their reasoning for adding the ingredient appeared to imply a claim.

Mr. Brown once again related to us that he had met with Dr. Jennings and promised him the results of reevaluating the x-rays on the Goshen cereal study. He added that the reevaluation was in progress and was almost completed.

Mr. Brown gave Dr. Gyarfas two manuscripts to peruse and stated that they were on the Elkhart, Indiana, beverage studies and would soon be published in one of the journals.

Quite a bit of discussion followed on the technicality and legality of publishing results of a study conducted under an IND without submitting the results first to the IND. It was brought out that the sponsor's interpretation of the results may possibly be different from FDA's evaluation of the data and hence might mislead the public.

Mr. Brown read the synopsis of both papers and requested that we review them and let the sponsor know what additional back-up data is needed.

Dr. Gyarfas informed our visitors that the papers should refer specifically to the IND under which the studies were conducted and should be in the form of an official submission.

Mr. Brown informed us that there had been an inquiry from Senator Edward Kennedy's office on the results of the Elkhart, Indiana, beverage studies—namely the "Kool-Aid" and "Tang" studies.

Dr. Gyarfas replied that we had a similar request for information from Senator Kennedy's office and that we informed his office that we could not give him any information because we had no data on the results of the studies in question. He further emphasized that even if we had the results the confidentiality of the sponsor had to be respected according to the regulations.

Mr. Anderson elaborated on this point also and expressed FDA's position in such a matter.

Mr. Brown also read a letter from FTC requesting the same information.

Dr. Gyarfas once again requested that the sponsor submit all the raw data and the summarized results of on each subject in each of the studies conducted under the seven IND's which the sponsor has discontinued.

Mr. Brown argued that until recently he had not been asked for individual patient records, but only for progress reports.

Dr. Gyarfas observed that this information had been requested several times in conference and only promises resulted. He pointed out that the Congressional inquiry as well as the sponsor's decision to add the active ingredient to their beverages without FDA reviewing the data, now makes it mandatory that they submit all raw data which should be in the form of individual patient record forms.

Mr. Anderson explained to our visitors FDA's position on releasing information to Senator Kennedy's office and FTC. He re-emphasized that the sole responsibility of release of such information lies with the sponsor.

Mr. Anderson then asked our visitors if they would give us a definite date by which this raw data on each IND will be submitted.

Mr. Brown conferred with Mr. Engle, from Indiana University, and Dr. Dykstra and agreed to have the data in by May 31, 1971.

Mr. Brown re-emphasized that at this time the company did not feel that there was sufficient basis in any of the IND's to file an NDA.

Dr. Gyarfas reluctantly accepted the two manuscripts, after much insistence from Mr. Brown, and stated he would file them in IND 3635 with their approval since no specific IND number or product was mentioned.

Mr. Brown thanked him and the conference ended with the usual amenities at 12:40 P.M.

CLARENCE C. GILKES, D.D.S.

ITEM 665

Enamel Protective Factors in Foodstuffs. M. E. Weiss,* B. H. Clarkson and H. Berlin. Eastman Dental Center, Rochester, New York; Lewistown, Pennsylvania.

Three methods: (1) half tooth decalcification; (2) solubility of radioactive enamel in bacterial fermentation products; and (3) an enamel surface "window" technique, were used to test extracts of plant materials for effects on enamel solubility. Using (1) it was found that 15 plant extracts offered a measure of protection against enamel dissolution in pH 4 lactic acid. With (2) solubility reductions of more than 90 percent were obtained with several herb products. With (3) levels of enamel protection were lower but quite definite. Tests designed to indicate how the extracts modified enamel solubility showed both organic and inorganic agents were involved; in method (2) inhibition of bacterial activity played a large part, and that in (3) where bacterial activity was not involved the enamel protection depended partly on inorganic (buffering) agents and the action of some organic components.

ITEM 666

Suppression of dental caries by chemical activation of the hypothalamic-parotid endocrine axis. R. R. STEINMAN* and J. LEONORA, Loma Linda University, Loma Linda, California.

Preliminary evidence suggests that the direction of fluid movement through the dentin plays a major role in resistance to dental caries. Fluid movement in the dentin is hormonally controlled by the hypothalamic-parotid gland axis. Components of the ornithine cycle, particularly urea, stimulate the hypothalamic-parotid axis which activates fluid movement through the odontoblastic processes in the dentin. The present study was conducted to determine whether the continuous chemical activation of the hypothalamic-parotid axis with subcutaneous (sc) administration of exogenous urea or citrulline would decrease the incidence of dental caries in rats maintained on a high sucrose cariogenic diet for 13 weeks. Seventy-six male Sprauge-Dawley 21 day old rats were divided into five groups and treated as follows: Group I twenty rats saline sc 3 times a day; Group II seventeen rats 20 mg urea sc/100 gm body wt/2 times a day; Group III thirteen rats 80 mg urea sc/100 gm 3 times a day; Group IV twelve rats 240 mg urea sc/100 gm 3 times a day; Group V fourteen rats 60 mg citrulline sc/100 gm 2 times a day. The number of cavities after 13 weeks was 15.6 ± 1.7; 9.9 ± 1.3; 4.5 ± 1.3; 1.8 ± 0.3; and 11.2 ± 1.5 respectively. All animals were autopsied. The animals receiving 240 mg urea 3 times a day showed evidence of stress having enlarged adrenals, spleen and kidneys and lower weight than the control animals. Those receiving 80 mg urea 3 times a day or less showed little or no evidence of stress.

ITEM 667

The Relative Effect on Dental Caries of Three Food Supplements to the Diet. Sidney B. Finn*, Homer Jamison, Institute of Dental Research, University of Alabama in Birmingham; School of Dentistry, University of Missouri, Kansas City, Missouri.

Over 600 children between 6 and 18 years of age in residence for 9 months of the year at a state institution, were divided into three equal groups of over 200 each. The three dietary additives were fed at the breakfast meal. All children consumed the same basic diet. Supplement one was a sugar-coated cereal; supplement two, raisins and fruit juices, and supplement three, a non sugar-coated cereal containing approximately 0.4% disodium phosphate incorporated into the cereal during the processing. Sugar and other sweets and carbohydrates in their daily diets were not restricted at any meal. After 18 months on these regimes, examinations with mouth mirror and explorer, and bite-wing radiographs revealed the following results. The mean DMF teeth or regime one was 1.57, regime two was 1.43 and regime three was 1.44. The mean DMF surfaces in regime one were 3.13, regime two 2.61 and regime three 2.89. Statistical analysis of these differences did not approach significant levels. Determinations based on the number of available surfaces did not reveal any significant differences either. This was a double blind study. The results would indicate that under the conditions of this study a sugar-coated cereal does not produce a significant change in dental caries incidence when compared to uncoated cereals or fruits containing natural sugars when eaten once a day in an unrestricted carbohydrate diet.

ITEM 668

Clinical Investigation of Dual Alloy Restorations in Teeth with Deep Subgingival Caries ELENA L. LIATUKAS*, College of Dentistry, Howard University, Washington, D.C.

A two-year study of gold-to-amalgam fillings restoring deep subgingival caries was made. The subgingival "problem" areas of caries were located both proximally and bucally. Forty adult permanent teeth were included in the study. In each case, a cast gold restoration was indicated but would have been technically difficult to construct due to caries depth. The technique used involved the buildup of gingival floors above soft tissue height with Ag amalgam prior to construction of the cast gold fillings. Extreme care was taken to position the gold to amalgam margins above the gingival crest for ease of clinical evaluation. Saliva pH was measured at pre- and post-restoration intervals. Other post-insertion clinical evaluations included: corrosion, discoloration, pitting, metallic taste and other discomfort related to the restored teeth. No significant change in pH occurred between pre- and post-insertion measurements (range 6.8–7.1). Surface discoloration was seen in two cases only at the 6 month interval. Discoloration observed was easily removed with prophylactic paste. Metallic taste occurred in one patient only following placement; however, spontaneous disappearance occurred after 1 month. No clinically significant changes in surface texture, marginal adaptation or corrosion were found in the cases tested. Microevaluations of these properties are being conducted.

Laboratory Studies* Concerning the Effect of Acid-Containing Beverages on Enamel Dissolution and Experimental Dental Caries

(By James L. McDonald, Jr., and George K. Stookey, Oral Health Research Institute, Indiana University-Purdue University at Indianapolis, Indianapolis, Indiana)

Studies were conducted to determine if acid-containing beverages affect adversely in vitro enamel dissolution and experimental dental caries, and if the addition of phosphate influences these systems. Results suggest that these beverages cause dissolution of enamel and produce enamel erosion in rat molars, regardless of the presence or absence of sucrose. Addition of NaH_2PO_4 reduced the damage to enamel.

For many years the literature has suggested that a variety of different acids are harmful to the teeth. McClure (1) noted that a dilute solution of lactic acid resulted in gross destruction of enamel and dentin. Similarly, Gortner, Restarski, and McCoy (2) observed extensive erosion of rat enamel one week after the ingestion of a soft drink that contained phosphoric acid; they suggested (3)(4) that this phenomenon was related to the type of carbohydrate in the beverages and the pH. Also, it was found (5) (6) that not only was erosion apparent with systems that contained various carboxylic acids (such as citric, acetic, and lactic acids), but similar findings were obtained with orange juice. Although it has been suggested (2), (7) that the presence of sucrose has a role in this process, it is more commonly accepted (8), (9) that the type of acid present and the hydrogen ion concentration are the dominant factors. It also has been suggested (10) that the influence of sucrose may be related more closely to the consumer properties of the beverage, and thus serves to increase the amount of damage found in vivo through an increased consumption. This damage can be manifested as erosion of the sound enamel surface or as an increase in dental caries in experimental animals.

Investigations as to which acids are most harmful have not resulted in clear-cut evidence, but it is known that damage is not directly proportional to the hydrogen ion concentration. Wynn and Haldi, (7) for example, studied the erosive action of various fruit juices in rats; they reported that the lack of relationship between the extent of erosion and the degree of acidity of the different juices indicates that there are other factors besides acidity that produce enamel damage. Generally, it is believed that a fruit juice prepared from fresh fruit is more injurious than the use of the fruit itself. (11)

Additional confirmatory reports about the adverse influence of acid-containing beverages on enamel have continued to appear in the dental literature. These reports expressed concern about the potential damaging effect of acid-containing

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soft drinks (12) and various fruit juices. (13) (15) Brunel et al (14) found an increased incidence of dental caries in rats that were given cider, which suggests that these preparations are not only erosive to enamel but may be cariogenic.

In addition to the investigations of the erosive properties of acid-containing beverages, as evidenced by in vitro experiments and studies in experimental animals, there have been clinical reports in which erosion was associated with the ingestion of these preparations. Finch (16) reported that extensive severe erosion is associated with the increased ingestion of citrus fruit drinks and fruit juices. Allan (17) found that extensive erosion was attributable to the ingestion of lemon juice.

Some of the previous in vitro studies (13) implied that the addition of calcium and phosphate to acid-containing systems would alleviate partially the chemical process of erosion. This effect was explained on the basis of the well-known buffering ability of phosphates, and the influence of the calcium and phosphate ions in the reduction of enamel dissolution by the common ion effect. There have been numerous studies (18)(19) about the beneficial influence of phosphates on dental caries in experimental animals and humans; thus, their possible role in the alleviation of erosion merits additional consideration.

Because acids, as such, are not commonly ingested, the practical problem involves the use of foods, candy, and beverages that contain specific acids as natural ingredients or those to which acids are added for purposes of taste or product stability. This series of studies was conducted to investigate the effect of commercially available, low pH food items on erosion and experimental dental caries and to determine if the addition of phosphate had a beneficial influence on this phenomenon. The results of the laboratory studies are reported in this paper, and the findings of studies with humans will be summarized in a paper (20) to be published.

MATERIALS AND METHODS

In vitro enamel decalcification (studies 1A and 1B).—To determine the influence of acid-containing foods and individual acids on enamel dissolution, two in vitro studies were conducted with the use of bovine incisor enamel that had been stored in a 2.8% Formalin solution (pH 7). The enamel sections were embedded in wax and cold-curing methyl methacrylate, and a circumscribed area 6 mm in diameter remained exposed. The teeth were placed in individual bottles to which 25 ml of the respective acid solutions was added and they were maintained in a continual immersion apparatus that revolved at 3 rpm for 24 hours. Two teeth were tested per group. The enamel sections then were removed and the solutions were analyzed for calcium by atomic absorption spectroscopy.

In vivo enamel erosion (study 2).—Sixty weanling male Wistar rats that weighed about 50 gm each were separated into four equal groups according to body weight. During the four-week experimental period, all rats were provided with a corn particle diet* and the following drinking solutions ad libitum: group 1, a sucrose-containing powdered soft drink mix (SC–PSD mix); group 2, SC–PSD mix plus 0.125% NaH_2PO_4; group 3, a powdered breakfast orange drink mix (PBOD mix); and group 4, PBOD mix plus 0.125% NaH_2PO_4. At the end of 28 days, the rats were killed, the heads were removed, and the soft tissue was dissected surgically from the jaws. The jaws then were stored in 10% neutral Formalin for two days, transferred to 70% alcohol for two days, and examined for the presence or absence of enamel erosion with the aid of a binocular microscope (X20). The severity of erosion was graded as follows: The lingual surface of each maxillary molar was separated mesiodistally into three different regions for scoring. In the mandible, the first molar was separated similarly into three different regions, whereas the second and third molars each were separated into two different regions for erosion evaluation. Thus, a total of 32 scores were obtained (one for each individual region) for the maxilla and mandible combined. Each region to be scored was assigned a value from 0 to 5 based on the following scale: 0, no erosion; 1, slight erosion limited to the enamel; 2, spot erosion with exposed dentin; 3, lingual enamel gone (self formation†); 4, erosion that extended onto the buccal surface; and 5, massive erosion with reduction in cusp height and tooth volume. The mean value for each maxillary tooth was added to the mean value for each mandibular tooth, which equalled the total mean severity score per rat.

* The composition of this diet was as follows (in percent): yellow corn meal, 64.0; powdered whole milk, 30.0; alfalfa meal, 4.8; iodized salt, 1.0; and irradiated yeast, 0.2.

† Characteristically, the observed erosion occurred almost exclusively on the lingual surfaces. In instances where all the enamel was eroded away from the clinical crown on the lingual surface, a shelf of enamel was left at the height of the gingival crest that had been present.

Experimental dental caries.—Sixty weanling male Wistar rats were separated equally into two groups (study 3*A*). The rats were provided with a cariogenic diet‡ ad libitum. The rats in group *A* served as controls and received distilled water ad libitum, whereas the rats in group *B* were given PBOD mix as the drinking beverage. This latter beverage was prepared fresh daily. After 60 days, the rats were killed and their heads were prepared for caries examinations as described previously (21).

Seventy-five weanling male Wistar rats were separated by body weight into three equal groups (study 3*B*). The rats were provided with the cariogenic diet ad libitum. The rats in group *A* served as controls and received distilled water ad libitum. The rats in group *B* received PBOD mix ad libitum (as in study 3*A*) instead of drinking water, whereas the rats in group *C* received PBOD mix fortified with 4.0 mg phosphate per milliliter, which was added as Na_2HPO_4. All drinking solutions were prepared fresh daily. The animals were maintained on these respective regimens for 42 days, at which time they were killed and their heads were prepared for caries examination as in study 3*A*.

One-hundred fifty weanling male Wistar rats were separated according to body weight into five equal groups (study 3*C*). All rats were given the cariogenic diet and the respective drinking water or beverages ad libitum. The rats in group *A* served as controls and received distilled water, whereas the rats in group *B* received a commercially available unsweetened orange juice in place of drinking water. The rats in group *C* were provided with commercially available sweetened orange juice. The rats in group *D* were given PBOD mix that was prepared fresh daily according to the manufacturer's printed instructions. The rats in group *E* received PBOD mix fortified with 1.0% $NaH_2PO_4H_2O$. The rats were maintained on these regimens for 42 days. At this time, the rats were killed by ether inhalation and the heads were examined for dental caries.

RESULTS

The data obtained in this study are indicated in Tables 1 through 6. Table 1 is a comparison of the amount of calcium that dissolved from enamel during a 24-hour immersion in a number of different carboxylic acid-containing foods and a comparison of the influence of the added phosphate in several instances. Although all of the evaluated products resulted in enamel dissolution, the greatest amount occurred with exposure to the sucrose-containing powdered soft drink mix; the least amount of dissolution occurred with exposure to the two dessert preparations. The addition of 1% NaH_2PO_4 seemed to reduce the rate of enamel dissolution in each instance.

TABLE 1.—*Relative Influence of Carboxylic Acid-Containing Foods on Enamel Dissolution In Vitro With and Without Added Phosphate (study 1A)*

Food item	*Enamel dissolution (μg Ca/ml/2½ hours)*
Water (distilled)	0
Sucrose-containing powdered soft drink mix	282
Sucrose-containing powdered soft drink mix + 1% NaH_2PO_4	140
Artificially sweetened powdered soft drink mix	220
Artificially sweetened powdered soft drink mix + 1% NaH_2PO_4	147
Hard sour candy ball *	200
Hard sour candy ball *	147
Hard sour candy ball * + 1% NaH_2PO_4	147
Powdered breakfast orange drink mix	111
Gelatin-type dessert	65
Instant dessert preparation	26
Apple juice	127

* One candy ball used per 50 ml water.

In Table 2, the influence of different carboxylic acids, which are used commonly in acidic food items, on enamel dissolution is compared. All of the acids resulted in enamel dissolution, but fumaric acid was more deleterious than either citric or tartaric acid at equivalent concentrations. The addition of phosphate to the three acids that were tested provided a small reduction in the amount of enamel dissolution that occurred.

‡The composition of this diet was as follows (in percent): yellow corn grits, 46.0; powdered whole milk, 28.5; sucrose, 19.5; alfalfa meal, 4.8; iodized salt, 1.0; and irradiated yeast, 0.2.

TABLE 2.—*Relative influence of phosphate in vitro enamel dissolution produced by commonly used carboxylic acids (study 1B)*

Carboxylic acid system	*Enamel dissolution (μg Ca/ml/24 hours)*
Fumaric acid (0.15%)	257
Fumaric acid (0.15%)+1% NaH_2PO_4	207
Citric acid (0.15%)	167
Citric acid (0.15%) + 1% NaH_2PO_4	123
Tartaric acid (0.15%)	159
Tartaric acid (0.15%) + 1% NaH_2PO_4	143

The results of the enamel erosion study in which the SC-PSD and PBOD mix were tested in rats are indicated in Table 3. The rats that received SC-PSD mix had higher erosion scores than those that received PBOD mix. The addition of NaH_2PO_4 at the 0.125% level reduced the erosion produced by both of these acid-containing beverages, although the differences between groups were not significant statistically ($P<0.06$).

The results obtained from the dental caries examinations of the rats in study 3*A* are indicated in Table 4. The control rats (group *A*) had an average of 8.1 lesions, whereas those in group *B*, which received PBOD mix, had an average of 11.6 lesions. The 43.2% difference in the incidence of caries is highly significant ($P<0.001$).

The data obtained from the rats of study 3*B* are shown in Table 5. The rats in group *B* that received PBOD mix in place of drinking water had an average of 12.1 lesions per rat; this was almost twice as many as the distilled-water control rats (group *A*), which had an average of 6.3 lesions. The mean number of lesions observed in the group *C* rats provided with phosphate-fortified PBOD mix was 5.5. A statistical evaluation of the data indicates that the increase in caries incidence in the rats provided with PBOD mix was highly significant ($P<0.001$) as compared with those given distilled water. Similarly, the addition of phosphate to this preparation (group *B*) resulted in a highly significant ($P<0.001$) anticariogenic effect. There was no significant difference between the distilled water group and the group that received the phosphate-fortified PBOD mix.

TABLE 3.—EFFECT OF 2 DIFFERENT CARBOXYLIC ACID-CONTAINING BEVERAGE MIXES ON ENAMEL EROSION IN THE RAT (STUDY 2)

Group	Regimen [1]	Number of rats	Mean weight gain (gm)	Mean total erosion score
1	SC-PSD mix	15	[2] 87.1±4.1	48.1±4.4
2	SC-PSD mix + 0.125 percent NaH_2PO_4	15	88.7±4.7	36.6±4.3
3	PBOD mix	15	84.2±8.1	11.4±3.0
4	PBOD mix + 0.125 percent NaH_2PO_4	15	87.4±5.8	4.8±1.4

[1] SC-PSD mix, sucrose containing powdered soft drink mix; PBOD mix, powdered breakfast orange drink mix.
[2] Standard error of the mean.

TABLE 4.—EFFECT OF A CARBOXYLIC ACID-CONTAINING PREPARATION ON CARIES IN RATS (STUDY 3A)

Group	Beverage consumed	Final number of rats	Average number of lesions	Percentage difference
A	Distilled water	28	[1] 8.1±0.3	
B	PBOD mix [2]	29	11.6±.4	[3] +43.2

[1] Standard error of the mean.
[2] Powdered breakfast orange drink mix.
[3] Value significant at 0.001 level.

TABLE 5.—EFFECT OF A CARBOXYLIC ACID-CONTAINING BEVERAGE MIX ON CARIES IN RATS (STUDY 3B)

Group	Beverage consumed	Final number of rats	Mean number of lesions	Percentage difference
A	Distilled water	22	[2] 6.3±0.5	
B	PBOD mix	21	12.1±.5	+92.1
C	PBOD mix + NaH_2PO_4	22	5.5±.7	−12.7

[1] Compared with distilled water control.
[2] Standard error of the mean.

The incidence of caries in study 3*C* is summarized in Table 6. The control rats that received distilled water had 7.7 carious lesions, whereas those provided with unsweetened orange juice had a numerically (but not statistically significant) lesser caries incidence of 6.6 lesions. The ingestion of sweetened orange juice (group *C*) resulted in 8.5 lesions per rat, which was slightly more than that of the control rats. The rats given PBOD mix had a mean value of 9.2 carious lesions; when compared with the control value, the latter finding represents a highly significant ($P<0.001$) increase in the incidence of caries (32%), which is attributable to the ingestion of the beverage. The provision of phosphate-enriched PBOD mix (group *D*) resulted in a mean value of 6.6 carious lesions. The addition of phosphate resulted in a highly significant ($P<0.001$) decrease in the incidence of caries (28.3%) when compared with that found in the rats provided with the commercially available preparation. Again, there was no significant difference in the caries experience of rats provided with distilled water and those given the phosphate-containing PBOD mix.

DISCUSSION

The results of this study confirm the findings of other investigators (1–16) which have illustrated the deleterious effect of low pH beverages on enamel. These data may or may not be related to damage that could result in the human, even though the erosion did occur in the rat and in vitro. These findings also indicate that various acidic foods differ in the magnitude of their deleterious effect on enamel. However, the absence of sucrose from these beverages does not render them harmless to enamel. Furthermore, all of the commercial products evaluated seemed to cause enamel dissolution, regardless of the presence or absence of sucrose in the product. Of course, the microbial metabolism of sucrose would be at a minimum at the low pH values present in some of these products. Thus the majority of the damage must be attributed to the constituent acids; the dentist should be aware of the damage caused by any food product that contains these acids, in spite of the rationale that they are cleared rapidly from the oral cavity.

TABLE 6.—EFFECT OF A CARBOXYLIC ACID-CONTAINING BEVERAGE MIX AND ORANGE JUICE ON CARIES IN RATS (STUDY 3C)

Group	Beverage consumed	Final number of rats	Average number of lesions	Percentage difference
A	Distilled water	28	[1] 7.7±0.5	
B	Unsweetened orange juice	28	6.6±.5	−14.3
C	Sweetened orange juice	27	8.5±.7	+10.9
D	PBOD mix	25	9.2±.5	[2] +19.5
E	PBOD mix+$NaH_2PO_4H_2O$	28	6.6±.4	[3] +14.3

[1] Standard error of the mean.
[2] Value differs significantly from control value at 0.05 level.
[3] Added at amount estimated to provide the rats with about 25 mg of phosphorus daily or about 6.54 percent by weight with PBOD mix.

A variety of different phosphates are known to reduce experimental caries in the rat and hamster (18). The data obtained in this study suggest that phosphate also can be effective in the reduction of the enamel dissolution that results from the use of acid-containing beverages and hard candies. When NaH_2PO_4 was added to the different acid beverages or the hard candy solution, a partial inhibition of enamel dissolution was found. The phosphate seemed to be effective when it was added to the sucrose or nonsucrose-containing acid beverages.

The collective results of the influence of PBOD mix on the incidence of caries in the rat indicate that this preparation is cariogenic. In these three studies, the provision of this product resulted in increases in the incidence of caries of 43.2, 92.1, and 19.5%, respectively. In each instance, the increase in the incidence of caries was significant. These findings confirm those of Brunel et al, (14) in which a different acid-containing beverage (cider) was found to be cariogenic in the rat.

The experimental caries findings further indicate that the latter preparation is significantly more cariogenic than unsweetened orange juice (Table 6), and that the addition of phosphate to this beverage resulted in a significant decrease in the cariogenic properties of the beverage. The addition of phosphate in studies *3B* and *3C* resulted in reductions of the cariogenicity of PBOD mix of 54.5 and 28.3%, respectively. Perhaps even more significant is the finding that the addition of phosphate negated completely the cariogenic properties of the beverage. In both instances, numerically (but not significantly) lower caries scores were found in rats given the phosphate-enriched preparation than in those provided with distilled water.

CONCLUSIONS

A series of in vitro and in vivo studies was conducted to determine if carboxylic acid-containing beverages affected enamel dissolution, erosion, and experimental dental caries, and to determine if the addition of phosphate influenced these systems beneficially. The results of these studies suggest that these beverages cause the dissolution of enamel and produce erosion in rat molars. The deleterious potential of these beverages seemed to be present, regardless of the presence or absence of sucrose. The addition of phosphate reduced the magnitude of the damage to enamel. The findings with regard to experimental caries indicate that the cariogenic properties of a typical acid-containing beverage can be negated completely by the addition of phosphate.

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